The pulmonary hemodynamics and exercise in chronic obstructive pulmonary disease

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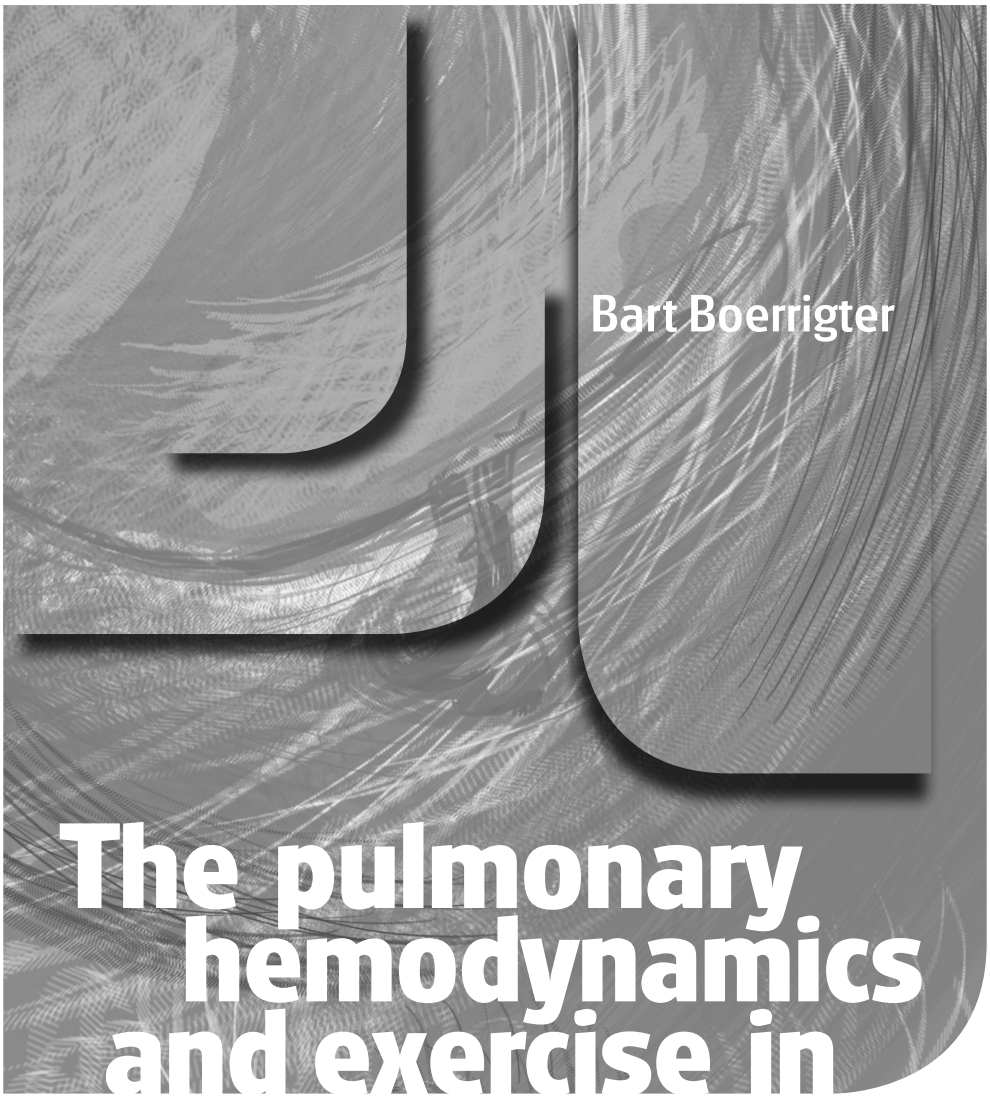

Bart Boerrigter

The pulmonary hemodynamics and exercise in chronic obstructive pulmonary disease

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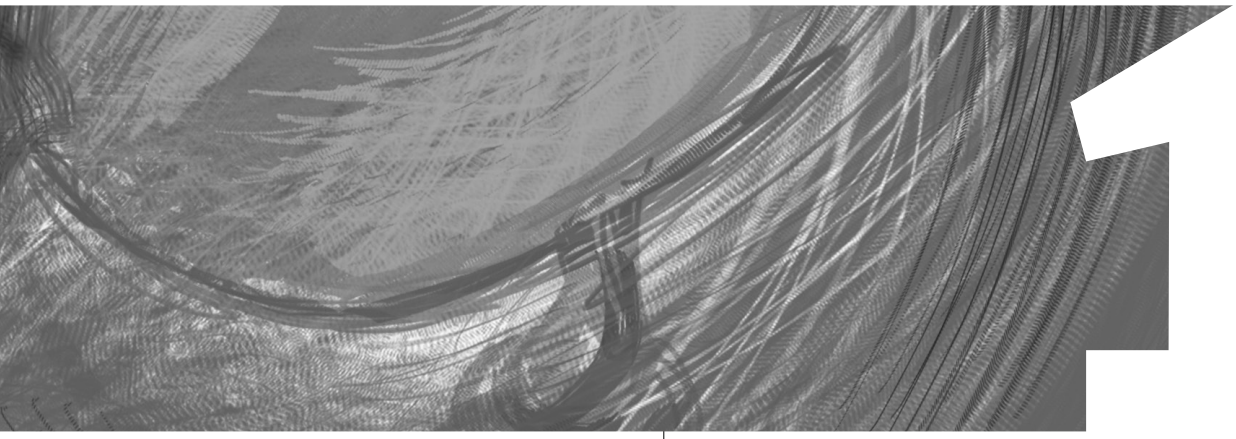
General Introduction and outline of the thesis



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CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is currently the fifth leading cause of death worldwide and predicted to be the fourth leading cause in 2030. (1) With worldwide an estimated prevalence of about 10% in the population over 40 years of age (2, 3), it represents a major economic and social burden. (4) COPD is defined as a common preventable and treatable disease characterized by persistent airflow limitation which is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. (4) COPD represents a mixture of small airway disease (obstructive bronchitis) and parenchymal destruction (emphysema) of which the relative contribution to chronic airflow limitation, varies between individuals (4).
Patients with COPD exhibit a markedly reduced exercise capacity which translates into a limitation in everyday life and activities, which is one of the main symptoms. (5) Improving exercise capacity is therefore one of the goals of treatment in patients with stable COPD. (4) A variety of mechanisms limiting exercise capacity can be found in these patients. Factors in COPD contributing to limited oxygen transport to the muscles and thereby curtailment of exercise capacity are abnormalities in ventilatory mechanics, gas exchange, oxygen transport and the function of respiratory and peripheral muscles. The contribution of the different mechanisms is likely to differ between patients.

VENTILATORY MECHANICS

Abnormalities in ventilatory mechanics during exercise are thought to be the most important contributor to the impaired exercise capacity in the majority of the patients. (6) In many patients the airflow limitation causes ventilation to reach its maximum before the cardiovascular limit is reached, while healthy subjects still show reserve in ventilatory capacity and exercise is rather stopped due to limits in maximal cardiac capacity. The mechanism of exercise impairment by airflow limitation has been subject of many studies. (7, 8) Dynamic hyperinflation, defined as a temporary increase in end-expiratory lung volumes, caused by an incomplete expiration. (figure 1.1), is thought to be important in the development of exertional dyspnea and exercise impairment. The incomplete expiration is the result of the exercise-induced increase in respiratory frequency in combination with an expiratory flow limitation. Hyperinflation can be seen as a compensatory mechanism, because airway resistance is lower at higher lung volumes. (9). However, hyperinflation may reduce maximal tidal volumes. In addition, hyperinflation forces the respiratory muscles to generate a lower pressure during inspiration and a higher pressure during expiration to overcome these higher lung volumes. The resultant higher 'work of breathing' contributes to sensation of dyspnea. (10) Lately tidal volume constraint during exercise, whether or not induced by dynamic hyperinflation, has been recognized as a major determinant of exercise capacity. Tidal volume constraint was shown to be strongly related to the onset and intensity of dyspnea and the termination of exercise. (11, 12). Hyperinflation is also thought to have adverse effects on the pulmonary circulation and may therefore influence exercise capacity in an additional way. The effect on the circulation is described below.

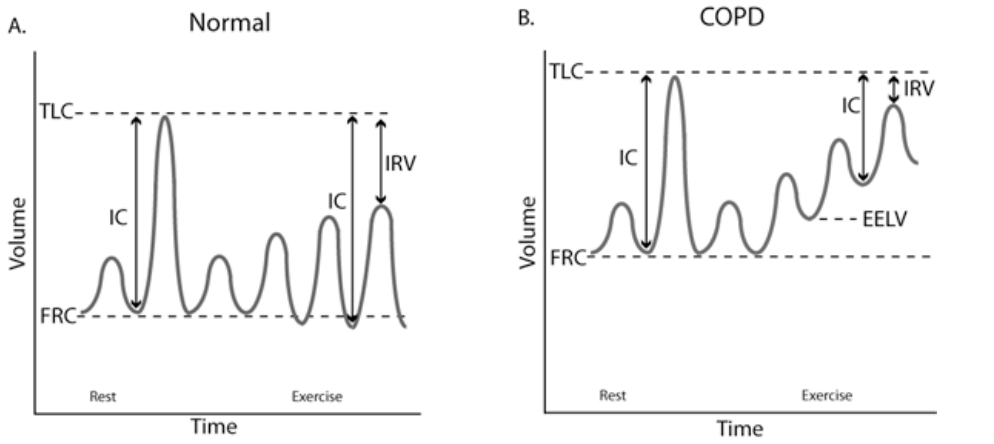

Figure 1.1 *Illustration of lung volumes at rest and during exercise in a healthy subject (A) and a COPD-patient (B). Patients with COPD have a higher functional residual capacity (FRC) at rest (static hyperinflation) and the now-called end-expiratory lung volume further increases during exercise (dynamic hyperinflation). The higher EELV causes an impaired ability to increase tidal volume (Vt) as the inspiratory reserve volume (IRV) minimizes. This in contrast to the normal situation, were the EELV decreases or remains stable during exercise which allows Vt to increase sufficiently during exercise with a larger IRV. The increase in EELV during exercise can be calculated by measuring inspiratory capacity (IC) and subtracting it from total lung capacity (TLC), as the latter remains constant during exercise.*

THE PULMONARY CIRCULATION

The altered pulmonary circulation in COPD is an potential cause of exercise impairment. In COPD stroke volume at rest is low (13) and the stroke volume increase to exercise is impaired. (14, 15) As a consequence, an increased ratio of heart rate to oxygen consumption is a frequently found abnormality. Several pathophysiological changes could influence the pulmonary circulation in COPD and limit cardiac function and oxygen transport. These changes are: 1) increased vascular resistance and right ventricular dysfunction, 2) left ventricular dysfunction and 3) effects of altered pulmonary mechanics on the circulation. An overview of the changes in pulmonary circulation can be found in figure 1.2.

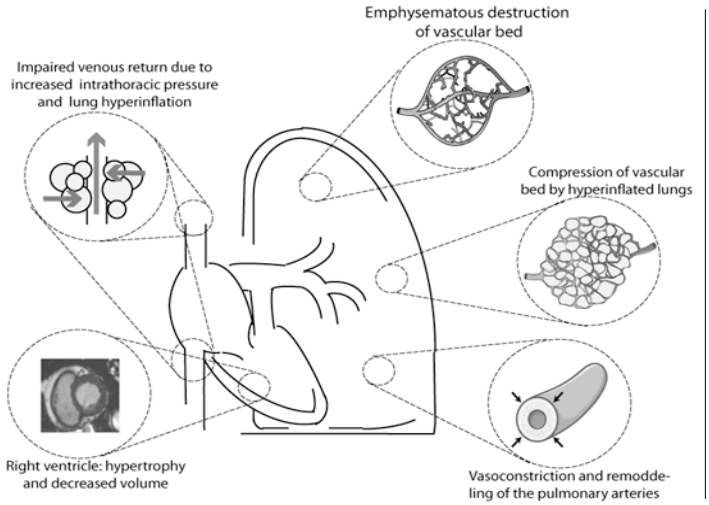

Figure 1.2 *Potential alterations of the pulmonary circulation and right ventricle due to COPD. Parts of this figure were produced using Servier Medical Art (www.servier.com).*

Changes of the pulmonary vascular bed.

Remodelling of the pulmonary arteries (figure 1.3), hypoxic vasoconstriction and emphysematous destruction of the vascular bed increase the pulmonary vascular resistance in COPD. (16, 17) Therefore, many patients show an elevated pulmonary artery pressure. The increases in resistance and pressure in the pulmonary arteries are often mild, but in a substantial part of the patients pulmonary artery pressure rises above 25 mmHg, the current definition of pulmonary hypertension (PH). In a relatively small amount of patients the pulmonary hypertension is severe and out-of-proportion with the severity of airflow limitation. In a large series of 998 hospitalized patients, the pulmonary artery pressure was ≥ 25 mmHg and ≥ 35 mmHg in respectively 50% and 5,8 % of the patients. (18) In a group with more severe airflow limitation, listed for lung transplantation or volume reduction surgery, the pulmonary artery pressure was 25-35 mmHg, 35-45 mmHg and ≥45 mmHg in respectively 36.7%, 9.8% and 3.7% of the 215 patients.(19, 20) Although the progression of pulmonary hypertension in COPD is slow (21) , it is shown to be a strong prognostic marker in patients with and without long-term oxygen therapy (22, 23).

As mentioned, only a few patients have pulmonary hypertension at rest. However, when cardiac output increases during exercise, a further increase in pulmonary artery pressure (20, 24) results, because the pulmonary vascular resistance does not decrease during exercise as it does in healthy subjects. There is currently no definition of exercise-induced pulmonary hypertension (25). High pulmonary artery pressures during exercise are predictive of developing resting pulmonary hypertension in COPD. The increased afterload, at rest or during exercise, might lead to a decreased right ventricular function, as measured by ejection fraction. (26, 27)

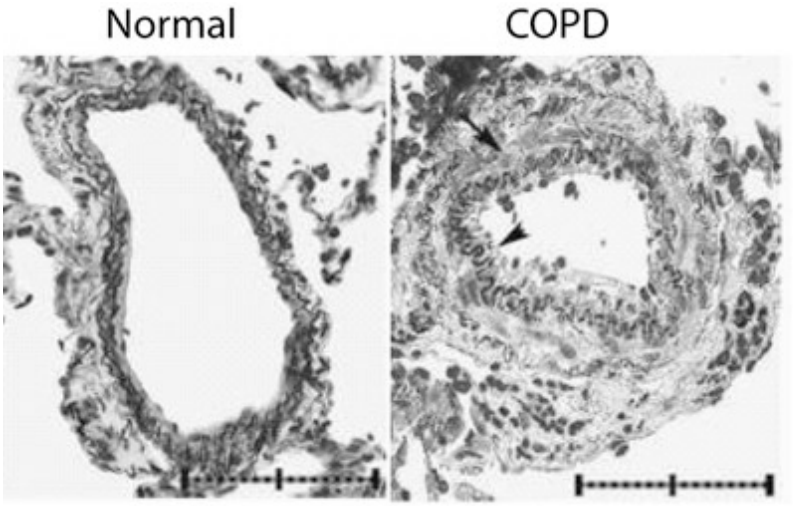

Figure 1.3 *Cross-section of a pulmonary artery from a healthy person and a COPD-patient. The three layers (intima, media, adventitia) of the small pulmonary arteries of wall show remodelling and increased thickness in COPD. The lumen of the vessels is decreased which increases resistance of the pulmonary vascular system. (picture from reference 17*

Systolic and/or diastolic dysfunction of the left ventricle are frequently found in the elderly population (28). And as the number one risk factor for COPD, smoking, is also risk factor for left ventricular dysfunction, it is not surprising that the two co-exist (29). However, in the absence of systemic hypertension or coronary artery disease, left-ventricular systolic dysfunction is usually absent in most patients with advanced COPD. The prevalence and significance of intrinsic diastolic dysfunction in COPD-patients is not well known as an increased RV afterload and RV dilatation (30) as well as a destroyed lung-architecture (31) may influence left ventricular diastolic function.

Circulatory effect of airflow limitation

When the pressure inside the thorax is increased, it leads to a lowered cardiac output. This results from a lowered venous return due to a lower pressure gradient for venous blood entering the thorax. (32) Patients on mechanical ventilation frequently require fluid administration to ensure sufficient venous return. (33) Patients with COPD develop high expiratory intrathoracic or pleural pressures, especially during exercise. (34) The pleural pressure during expiration is increased due to the combination of an increased airway resistance and decreased elastic recoil of the lungs. Due to the increased airflow resistance alveolar pressure, the driving pressure of expiratory airflow, has to be higher for a similar amount of airflow. The decreased elastic recoil requires generation of a larger part of the alveolar pressure by the expiratory muscles, thereby also increasing pleural pressure. It has been suggested a long time ago that the increased pleural pressure during exercise might also impair cardiac function in COPD-patients. (34) The potential negative effect of the increased pleural pressures on cardiac function may be enhanced by the compressive effects of hyperinflated lung on cardiac structures (31). In addition to the negative effects on venous return, pulmonary hyperinflation can also increase pulmonary vascular resistance by compression of the pulmonary vascular bed. (35, 36)

There is, however, only scarce literature on the venous return during spontaneous breathing in COPD-patients. Using angiography, Nakhjavan et al. (37) found disturbances in flow in the inferior vena cava at the level of the diaphragm. The timing of impaired blood flow in the respiratory cycle was not consistent, however. Later, these findings were confirmed by echocardiography (38). However, the effect of these phasic alterations in venous return on right ventricular output and especially its significance of it during exercise remains unknown.

In addition to studies which evaluated vena cava blood flow, echocardiography and cardiac MRI studies showed that patients with COPD have reduced right and left ventricular volumes at rest. (13, 39-41) This finding could be the result of a decreased venous return by altered pulmonary mechanics, as the reduction in ventricular volumes is related to the amount of hyperinflation (42). Hyperinflation is also shown to cause a lower oxygen pulse, an estimate of stroke volume, during exercise. (43, 44) Some studies used a helium-oxygen mixture (lower density and generates therefore lower resistance) to evaluate the effects of airflow limitation on cardiac function. However, mostly non-invasive methods were used and outcomes were variable. Heliox improves the airflow in case of airway obstruction without direct effects on the pulmonary vasculature and the heart. In some studies breathing heliox was associated with improved heart-rate kinetics and oxygen delivery, non-invasive estimates of cardiac function (45, 46). Other studies did not find improvements in stroke volume despite improved airflow with heliox during exercise (47, 48).

CONTRIBUTION TO EXERCISE INTOLERANCE

As described above, patients with COPD have several reasons for impaired an stroke volume and cardiac output. However, just the fact that maximal cardiac output or stroke volume is lower during exercise does not necessarily mean that the impaired cardiac function leads to early termination of exercise. The rise in pulmonary artery pressure or the effects of increased intrathoracic pressure on the circulation during exercise seem to be mostly present in patients who also exhibit a severely impaired ventilatory capacity. It is important to realize that two different scenarios can be present at maximal exercise. 1) Maximum cardiac output and stroke volume do not reach their maximum as compared to normal as a result of early termination of exercise when patient reaches maximal ventilation. 2) Cardiac output reaches its maximum and is the cause of exercise termination. Moreover, a faster increase in heart rate or a lower stroke volume with exercise does not always translate into exercise intolerance. When evaluating the cardiac function during exercise of COPD-patients, it is essential to take into account the amount of work or oxygen consumption and the reserves in ventilation and cardiac output.
Evidence that abnormalities in the pulmonary circulation contribute to exercise intolerance comes from studies in which associations between pulmonary artery pressure at rest (49) or right ventricular parameters (50) and exercise capacity were found. On the other hand, several studies showed that although stroke volume during exercise is less than in healthy subjects, the increase of cardiac output for the amount of oxygen consumption increase during exercise (CO/VO_2-slope) is within normal limits (14, 51, 52). Additional evidence that pulmonary hypertension does not contribute to limited exercise capacity, at least in most patients, comes from studies who used pulmonary vasodilating therapies. Despite successful lowering of pulmonary artery pressure, exercise capacity was not increased. (53, 54)

AIM OF THIS THESIS

The aim of this thesis is twofold. First, we aimed to determine the effects of pulmonary hypertension and the circulatory effects of airflow obstruction on the pulmonary circulation in patients with COPD. Evaluation of the contribution of both is important as both abnormalities could potentially be treated by different strategies. Pulmonary hypertension may react to pulmonary vasodilating therapy. However, if the adverse, mechanical effects of airflow limitation are predominantly responsible for the impaired circulation, it is unlikely that vasodilating therapy will be beneficial. Secondly, we aimed to elucidate in which COPD-patients pulmonary hypertension is the cause of exercise termination. This identifies the patients in which the exercise capacity could potentially benefit from therapy aimed at the pulmonary circulation. The results of these studies are presented in this thesis.

In **chapter 2** we show how airflow limitation induces fluctuations in the pulmonary circulation and how it can impair stroke volume. In the appendix of **chapter 2** is explained how a forced expiration during a pulmonary function test severely influences the pulmonary circulation and cardiac function. In **chapter 3** we investigated the influence of intrathoracic pressure on stroke volume by an intervention with a helium-oxygen mixture aimed to improve airflow and lower intrathoracic pressure. That increases in intrathoracic pressure

during exercise can lead to errors in hemodynamic measurements is shown and how this can be corrected is shown in **chapter 4**. What amount of pulmonary hypertension leads to exercise impairment is evaluated in **chapter 5**. In **chapter 6** we describe two patients with the unfortunate combination of severe COPD and a patent foramen ovale, to illustrate the complex interaction between heart and lungs. In **chapter 7** we evaluate how pulmonary hypertension affects the size of the pulmonary artery in patients with pulmonary arterial hypertension. In **chapter 8** the findings of the previous chapters are summarized.

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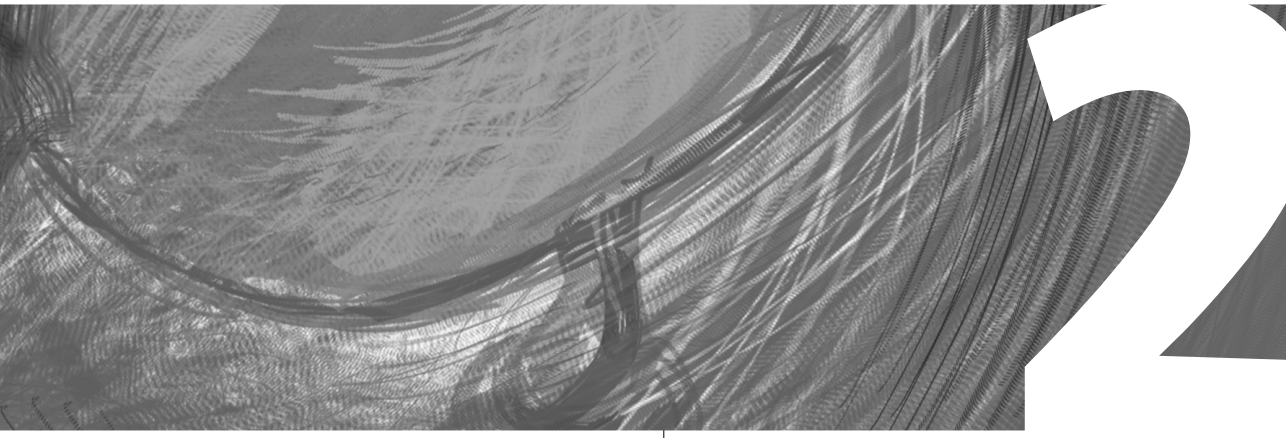
Right atrial pressure affects the interaction between lung mechanics and right ventricular function in spontaneously breathing COPD patients.



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ABSTRACT

Introduction

It is generally known that positive pressure ventilation is associated with impaired venous return and decreased right ventricular output, in particular in patients with a low right atrial pressure and relative hypovolaemia. Altered lung mechanics have been suggested to impair right ventricular output in COPD, but this relation has never been firmly established in spontaneously breathing patients at rest or during exercise, nor has it been determined whether these cardiopulmonary interactions are influenced by right atrial pressure.

Methods

Twenty-one patients with COPD underwent simultaneous measurements of intrathoracic, right atrial and pulmonary artery pressures during spontaneous breathing at rest and during exercise. Intrathoracic pressure and right atrial pressure were used to calculate right atrial filling pressure. Dynamic changes in pulmonary artery pulse pressure during expiration were examined to evaluate changes in right ventricular output.

Results

Pulmonary artery pulse pressure decreased up to 40% during expiration reflecting a decrease in stroke volume. The decline in pulse pressure was most prominent in patients with a low right atrial filling pressure. During exercise, a similar decline in pulmonary artery pressure was observed. This could be explained by similar increases in intrathoracic pressure and right atrial pressure during exercise, resulting in an unchanged right atrial filling pressure.

Conclusions

We show that in spontaneously breathing COPD patients the pulmonary artery pulse pressure decreases during expiration and that the magnitude of the decline in pulmonary artery pulse pressure is not just a function of intrathoracic pressure, but also depends on right atrial pressure.

INTRODUCTION

An imposed high intrathoracic pressure can depress venous return and subsequently right ventricular output [1,2], particularly in patients with a low fluid status [3,4]. In chronic obstructive pulmonary disease (COPD), airway obstruction leads to an increase in intrathoracic pressures during expiration due to the use of expiratory muscles and lung hyperinflation. It is unknown whether similar interactions between intrathoracic pressure, right heart filling, right heart output and fluid status exist in spontaneously breathing COPD-patients. Many patients with COPD have evidence of fluid retention and an increased right atrial pressure (RAP), and diuretics are frequently prescribed to restore fluid balance. It may be argued that spontaneously breathing COPD patients with a low right atrial pressure are more vulnerable for an impaired right heart filling during expiration, possibly translating into an impaired RV output. [5]

In order to better understand cardiopulmonary interactions in COPD, one would ideally measure beat-to-beat changes in right ventricular stroke volume over the respiratory cycle and relate changes in intrathoracic pressures to changes in stroke volume. Because such measurements are technically difficult, we used the decline in pulmonary artery pulse pressure to describe the effect of expiratory airflow limitation on RV return and output in spontaneously breathing COPD patients at rest and during exercise. We show that in COPD, like in patients on positive pressure ventilation, the interplay between intrathoracic pressure and right atrial pressure critically determines RV output.

METHODS

Patients

All patients participated in a study to investigate the effects of dynamic hyperinflation on the pulmonary circulation and right ventricular function and therefore underwent right heart catheterization and oesophageal pressure measurement at rest and during exercise. Eligible patients were diagnosed with moderate to very severe COPD, defined as an post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ≤0.7 and a FEV_1-value < 80% or predicted, according to ATS/ETS criteria [6] Exclusion criteria were a history of left sided cardiac failure, signs of left ventricular dysfunction and/or valvular disease on Doppler echocardiography, neuromuscular disorders or an acute exacerbation in the 4 weeks prior to inclusion.

This study has institutional review board approval (Medical ethical review committee VU University Medical Center, registration number: NL30766.029.10) and all patients were informed and gave written consent to the procedures.

For comparison we used data from patients with normal pulmonary function and normal pulmonary hemodynamics, analysed in our center for suspected pulmonary hypertension.

Right Heart Catheterization

A balloon-tipped, flow directed 7.5 Fr, triple-lumen Swan-Ganz catheter was brought, via the jugular vein, into position under local anaesthesia. The patients were in stable condition, lying supine and breathing room air, while heart rate was continuously monitored. The ports of the catheter were positioned in the right atrium, right ventricle and pulmonary artery. An arterial line was inserted in the radial artery.

Oesophageal Pressure

We continuously monitored oesophageal pressure, as a measure of intrathoracic pressure. A standard oesophageal balloon-catheter (Microtek Medical B.V. Zutphen, The Netherlands) was inserted transnasally with the use of lidocaine gel (2%) and positioned in the mid-oesophagus. Subsequently, 5 mL of air was injected into the balloon followed by the withdrawal of 4 mL to partially inflate the balloon. The pressure signal was checked and in case of cardiac beat artefacts the position of the balloon-catheter was slightly adjusted upwards. Pleural pressure measurements were not available in the group of control subjects, but careful inspection of the pulmonary artery and right atrial pressure curves allowed identification of in- and expiratory phases.

Protocol

With the Swan-Ganz catheter, oesophageal balloon-catheter and arterial line in position patients were placed on an electromagnetically braked cycle ergometer (Ergoline GmbH, Bitz, Germany), in supine position. The exercise protocol consisted of 3 minutes rest, followed by a progressively increasing work rate to maximum tolerance. Work rate was increased every 3 minutes until maximum. The different levels of exercise were based on a maximal exercise test performed the day before.

Measurements

Pressures in the right atrium, right ventricle, pulmonary artery, oesophagus and radial artery were simultaneously measured and digitally recorded using a PowerLab data acquisition system (ADInstruments). Oxygen consumption (VO_2) was measured during the entire protocol using a metabolic cart (Vmax 229, Viasys, Yorba Linda, CA, USA). At rest and peak exercise, measurements of pulmonary capillary wedge pressure (PCWP) and inspiratory capacity (IC) were performed and blood samples were collected. Afterwards, cardiac output (CO) obtained by direct Fick-method from arterial- and mixed venous oxygen saturation and VO_2. Pulmonary vascular resistance (PVR) was calculated as (mPAP - PCWP)/CO. Mean right atrial pressure and oesophageal pressure, both at end-expiration, were used for calculating right atrial transmural pressure (RAP_tm).

A semiautomatic program using Matlab R2008a (The MathWorks, Natick, MA) was used to acquire systolic and diastolic pressure in the pulmonary artery beat by beat over at least 10 consecutive respiratory cycles of the resting period and during the last minute of exercise. The decline in pulse pressure in the pulmonary artery was calculated as the pulse pressure of the last heartbeat during expiration (*pulse 2*) minus the pulse pressure of the first heartbeat during expiration (*pulse 1*) and represented as percentage of *pulse 1*. Mean pulmonary artery pressure was calculated on a beat-to-beat basis. The change in systolic pressure in the radial artery over the respiratory cycle was calculated as the lowest minus the highest systolic pressure.

Lung Function

Lung function measurements were performed within two days of the right heart catheterization. Static and dynamic lung volumes and diffusion capacity of carbon monoxide (DLCO) using a metabolic chart (Vmax 229, Viasys, Yorba Linda, CA, USA) were measured according to the European Respiratory Society guidelines [7,8].

Statistical Analysis

Lung function, exercise and hemodynamic values are presented as mean ± standard deviations. Comparison of rest and exercise was performed with a paired sample t-test. To evaluate the influence of RAP_tm on the decline in pulse pressure in the pulmonary artery a non-linear curve was fitted through the data points and correlation coefficients (r^2) were calculated. All tests were two-tailed and a P-value of <0.05 was considered significant. Analyses were performed with SPSS 15.0 for Windows (SPSS Inc, Chicago Illinois) or GraphPad-Prism for Windows (version 4.0)

RESULTS

Patient Characteristics

Twenty-one patients (13 female) with a mean age of 63 years were included in this study. Pulmonary function characteristics are shown in table 2.1.

Variable	Mean ± SD	% of predicted ± SD
FEV_1, L	1.49 ± 0.58	53 ± 16
FEV_1/VC, %	45 ± 11	
VC, L	3.33 ± 1.0	96 ± 20
TLC, L	6.53 ± 1.12	110 ± 17
RV/TLC, %	49 ± 12	
FRC, L	4.33 ± 1.0	141 ± 35
DLCO, mmol/kPA/min	3.86 ± 1.53	44 ± 15
PaO_2, mmHg	64 ± 14	
$PaCO_2$, mmHg	40 ± 8	

Table 2.1 Lung function characteristics
FEV1: Forced Expiratory Volume in 1st second, VC: Vital Capacity, TLC: Total Lung Capacity, RV: Residual Volume, FRC: Functional Residual Capacity, DLCO: Diffusion Capacity of the Lungs for Carbon Monoxide

In the study group FEV_1 ranged from 0.58 to 2.72 L. and the FEV_1/VC ratio ranged from 27 to 64 %. Based on the FEV_1 percent of predicted, 9 patients had moderate, 10 had severe and 2 had very severe airway obstruction. The resting and peak exercise metabolic parameters are shown in table 2.2. Maximal power ranged from 10 to 120 Watt, with a mean of 38 Watt. Peak VO2 and maximal ventilation (VEmax) were low compared to the predicted values. The hemodynamic measurements at rest and during peak exercise are summarized in table 2.3.

Variable	Rest	Peak Exercise
VO_2, mL/min	286 ± 65	841 ± 327 *
VO_2, ml/kg/min	3.8 ± 0.6	11 ± 3.45 *
VE, L/min	13 ± 3.4	35 ± 16 *
VE/MVV, %	42 ± 19	59.4 ± 16 *
Vt, L	0.73 ± 0.25	1.14 ± 0.56 *
RR, breaths/min	18 ± 4	32 ± 8 *
IC, L	2.20 ± 1.57	1.57 ± 0.55 *
Variable	**Rest**	**Peak Exercise**
VO_2, mL/min	286 ± 65	841 ± 327 *

Table 2.2 Exercise test parameters
*VO_2: Oxygen uptake, VE: Minute ventilation, MVV: Maximal Voluntary Ventilation, Vt: Tidal Volume, RR: Respiratory Rate, IC: Inspiratory Capacity, * p < 0.05 versus rest*

Variable	Rest	Peak Exercise
mPAP, mmHg	32 ± 14	57 ± 16 *
CI, L/m^2	3.3 ± 0.9	5.5 ± 1.5 *
HR, b/min	83 ± 16	120 ± 18 *
SVI, ml	40 ± 11	46 ± 12 *
PVR	348 ± 340	365 ± 308
mRAP, mmHg	7 ± 5	15 ± 6 *
PCWP, mmHg	9 ± 2	16 ± 5 *
SaO_2, %	91 ± 5	84 ± 9 *
SvO_2, %	63 ± 10	39 ± 8 *

Table 2.3 Hemodynamic parameters
*mPAP: mean Pulmonary Artery Pressure, CI: Cardiac Index, HR: Heart Rate, SVI: Stroke Volume Index, PVR: Pulmonary Vascular Resistance, mRAP: mean Right Atrial Pressure, PCWP: Pulmonary Capillary Wedge Pressure, SaO_2: Arterial oxygen saturation, SvO_2: Mixed venous oxygen saturation. * p < 0.05 versus rest*

Thirteen of the 21 patients were diagnosed with pulmonary hypertension (resting mean pulmonary artery pressure > 25 mmHg[9]. Cardiac index ranged from 1.4 to 4.7 L/min/m^2. During exercise pulmonary artery pressures increased significantly. The demographic, pulmonary function and hemodynamic characteristics of the control subjects are summarized in table 2.4.

Variable	
Male/Female	3/7
Age, yr	48 ± 10
Height, cm	169 ± 9
Weight, kg	76 ± 14
FEV_1, L	3.09 ± 1.12
FEV_1, % of predicted	108 ± 19
FEV_1/VC, %	77 ± 5
VC, % of predicted	112 ± 30
DLCO, % of predicted	95 ± 17
mPAP, mm Hg	17 ± 4
CI, $Lmin/m^2$	4.1 ± 0.8
PVR, $dyn/s/cm^{-5}$	88 ± 38

Table 2.4 Characteristics of control subjects
FEV_1: Forced Expiratory Volume in 1st second, VC: Vital Capacity, DLCO: Diffusion Capacity of the Lungs for Carbon Monoxide, mPAP: mean Pulmonary Artery Pressure, CI: Cardiac Index, , PVR: Pulmonary Vascular Resistance

Oesophageal and Transmural right atrial pressure.

End expiratory oesophageal pressure was 4 ± 4 mmHg at rest and increased to 12 ± 4 mmHg at peak exercise, showing expiratory airflow obstruction. End inspiratory pressure was -6 ± 3 mmHg at rest and decreased to -13 ± 3 at peak exercise. Mean right atrial pressure was 8 ± 4 mmHg and increased significantly with exercise to 17 ± 8 mmHg.
Transmural right atrial pressure (RAP_tm) during expiration ranged from 1 to 16 mmHg (mean 6) at rest. During exercise, oesophageal pressure and right atrial pressure increased with a similar amount and thus, RAP_tm during exercise was similar to RAP_tm measured at rest (see also figure 2.1).

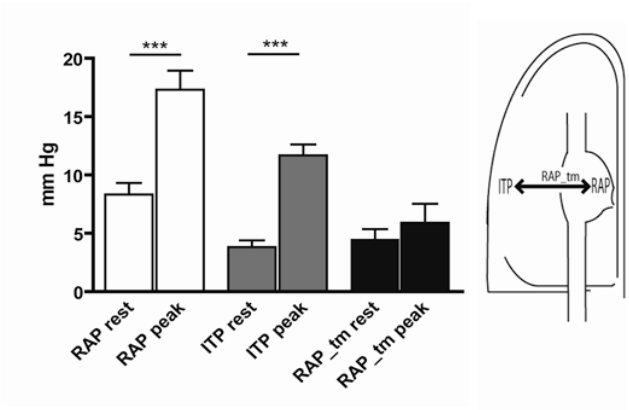

Figure 2.1 *The right atrial (RAP) and intrathoracic pressure (ITP) at rest and peak exercise. Note the rise in RAP and ITP as the transmural pressure of the right atrium (RAP_tm) remains constant. RAP_tm is calculated as pressure inside the right atrium (RAP) minus the pressure outside the right atrium, which is the ITP. *** = P<0.0001*

Expiratory pulse pressure decline in the pulmonary artery.

During expiration there was a decline in the pulmonary artery pulse pressure in all but one patient. The patient not showing a decline in pulmonary artery pulse pressure had severe pulmonary hypertension. The decline in pulse pressure as shown in figure 2.2 ranged from 0 to 41 % with a mean of 17% and was greatest in those patients with a low RAP_tm (see figure 2.3). The relationship between pulse pressure decline and RAP_tm could be de-

scribed by a natural logarithmic curve (best-fit correlation; $r^2 = 0.61$). The decline in pulse pressure in the pulmonary artery during *expiration* was followed by a decrease in systolic radial artery pressure during *inspiration*, a phenomenon which is also known as pulsus paradoxus (see figure 2.2). The average expiratory decline in pulse pressure in the healthy subjects was -4.5 % ± 3.1 %, which was significantly lower than the pulse pressure decline in COPD-patients (unpaired t-test, p: 0.0012).

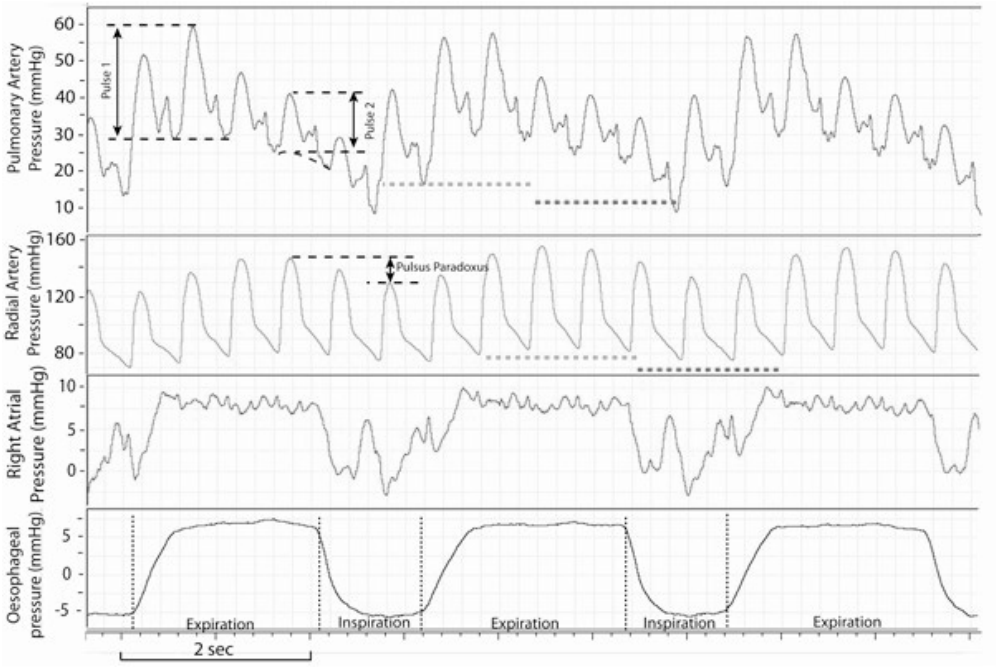

Figure 2.2 *Example of the behavior of the pulmonary artery pressure over the respiratory cycle in a COPD patient. In the upper channel we show the decline in pulse pressure (pulse 1 - pulse 2) in the pulmonary artery during expiration, which is a consistent phenomenon over all respiratory cycles. The second channel shows the pressure in the radial artery. The decline in pulse pressure in the radial artery seems to follow the decline in the pulmonary artery pressure. (red dotted lines). During expiration, the intrathoracic pressure (channel 4) probably exceeds the central venous pressure, which would explain the flat line of the right atrial pressure (channel 3).*

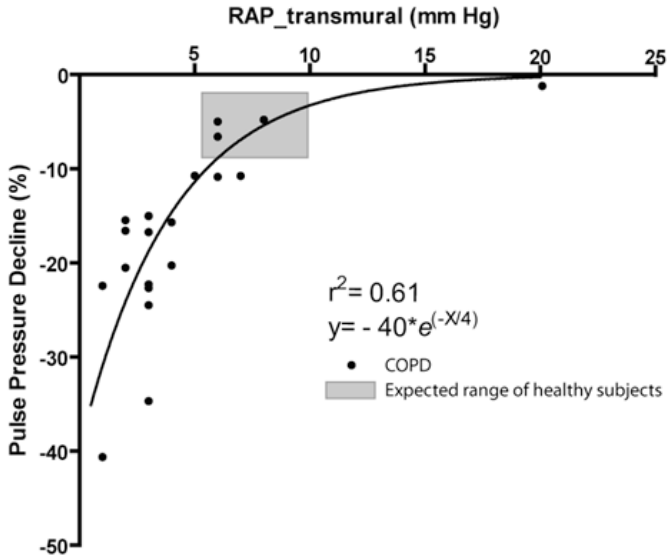

Figure 2.3 *Relationship between transmural pressure of the right atrium (RAP_tm) and the percent decline in pulse pressure in the pulmonary artery. Gray area represents the suspected window of normal, based on the calculated pulse pressure decline and the suspected RAP_tm of the control subjects.*

Expiratory pulse pressure decline during exercise

We subsequently examined the presence of similar relationships between intrathoracic, right atrial and pulmonary artery pulse pressures during exercise. As shown in figure 2.1, both right atrial pressure and intrathoracic pressure increased significantly during exercise, which resulted in an unaltered RAP_tm. With exercise, there was an expiratory decline in mean pulmonary artery pressure and pulmonary artery pulse pressure, ranging from 0 to 35% with a mean of 20%. Again, there was an exponential correlation between the expiratory pulmonary artery pulse pressure decline and RAP_tm ($r^2 = 0.52$).

DISCUSSION

This is the first study showing a significant interaction between intrathoracic pressure, right atrial filling and right ventricular output in spontaneously breathing COPD patients. Based on combined measurements of intrathoracic and hemodynamic pressures in 21 patients with moderate to very severe airflow obstruction, we show that the pulmonary artery pulse pressure decreases during expiration and that the magnitude of this decline is not just a function of intrathoracic pressure, but also depends on right atrial transmural pressure. The interaction between intrathoracic pressure, right atrial filling and right ventricular output is well known in mechanically ventilated patients: when high levels of positive airway pressure are required to maintain oxygenation, venous return may be impaired [3,4] and fluid administration may be necessary to prevent hemodynamic collapse.

Intrathoracic pressure is increased during expiration in patients with COPD, which leads to an impairment of caval blood entering the thorax [10,11]. Here we show the hemodynamic consequence, which is an expiratory drop in mean pulmonary artery pressure and pulmonary artery pulse pressure. Because the intrathoracic pressure remained unaltered and pulmonary arterial compliance can be considered constant during expiration [12], the drop in pulmonary artery pressure implies a decreased right ventricular stroke volume during expiration in COPD. While under physiological circumstances the RV and pulmonary circulation are capable of buffering most respiratory variations in venous return towards a near constant flow [13,14,15], the impairment of venous return during expiration seem to be exaggerated to such a degree that a drop in RV stroke volume and pulmonary artery pressure is created due to expiratory airflow limitation.

The decline of the pulmonary artery pulse pressure was largest in patients with a normal right atrial pressure (fig 2.3). A normal right atrial pressure in combination with a high intrathoracic pressure means a low transmural pressure of the right atrium. The pulsatility of the right atrial pressure during expiration decreased in patients with a normal right atrial pressure (fig 2.2), indicating a serious impairment of right atrial filling. In these patients the right atrial pressure equals the rise in intrathoracic pressure which is the major cause of a decline in venous return [16,17]. In contrast, the expiratory decline in pulmonary artery pulse pressure was attenuated or completely absent in COPD patients with a high right atrial pressure. As illustrated in figure 2.3 and exemplified in figure 2.4, a high pressured and dilated right atrium and caval vein can act as a reservoir maintaining constant RV filling during expiration despite any increases in intrathoracic pressure. In our study group the highest right atrial pressures were found in patients with pulmonary hypertension. In COPD patients with associated pulmonary hypertension, both RV afterload and preload are increased [18,19,20,21]. Paradoxically, in patients with COPD associated pulmonary hypertension, the impaired RV function seems to prevent a decline in RV output during expiration via distension of the right atrium. We found a natural logarithmic relationship between RAP_tm and the expiratory pulse pressure, which can be explained by the inability of the RAP_tm to reach negative values and the inability of the pulmonary artery pulse pressure change during expiration to reach positive values.

The average expiratory decline in pulse pressure in the 10 healthy subjects was -4.5 %. Right atrial pressure in these subjects was 5 ± 2 mm Hg. When we assume a pleural pressure at the end of expiration of -2 to -4 mmHg (as has been previously shown in healthy subjects [22]), the RAP_tm was between 7 and 9 mm Hg. These values fit nicely on the line drawn in figure 2.3. This range in RAP_tm may represent a window allowing optimal RV filling. It can be hypothesized that some degree of fluid retention in COPD is an adequate response to maintain RAP_tm close to the physiological window of 7 to 9 mmHg. Alternatively, it can be hypothesized that the higher RAP is just the consequence of an increased RV afterload.

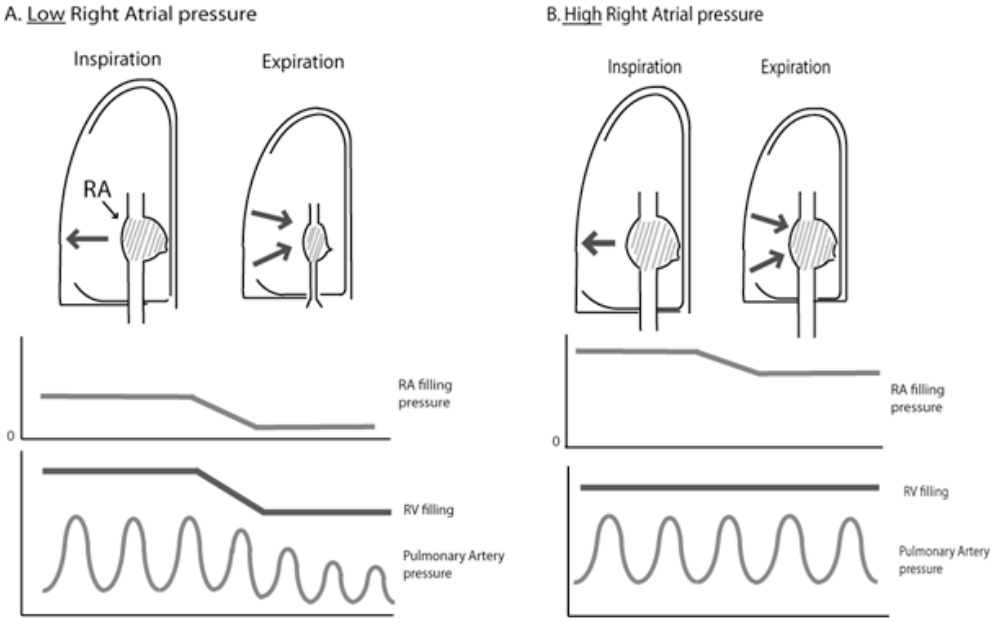

Figure 2.4 *Schematic illustration of the effect of similar intrathoracic pressures (blue arrows) on right atrial (RA) filling, RV filling and the pulmonary artery pressure in a situation of either a low (A) or high (B) right atrial pressure. When RAP is low, the positive intrathoracic pressure during expiration leads to an impaired venous return and a variation in RV filling and stroke volume during the respiratory cycle. When RAP pressure is high, the right atrium acts as a reservoir which maintains RV filling and ensures a stable pulmonary artery pulse pressure and RV stroke volume during expiration.*

We found a comparable interaction between intrathoracic and intravascular pressures during exercise, which is likely explained by the fact that the same hemodynamic mechanisms are at work at rest and during exercise (figure 2.1). The increase in RAP during exercise is likely the result of an increased intrathoracic pressure, leading to an unaltered filling pressure of right atrium. It has to be noted, however, that the patients in our study performed supine exercise and it is possible that during upright exercise (such as during normal daily activities), venous return may be lower. In this situation, the negative effect of a high intrathoracic pressure during expiration may be larger.

We observed a drop in systemic blood pressure over the respiratory cycle in all patients with an expiratory drop in pulmonary artery pulse pressure. The drop in pulse pressure in the systemic circulation followed about 2-3 heartbeats after the decline in the pulmonary artery pulse pressure and, therefore, occurred partially during inspiration (see fig 2.2). We did not study whether the changes in systemic pressure were causally related to the decline in the pulmonary artery pulse pressure, but it can be speculated that in patients with airflow obstruction part of the phenomenon of a pulsus paradoxus (>10mmHg drop in systemic pressure during *inspiration*), is due to an interaction between right and left ventricular performance. Recently, even mild COPD patients were shown to have a reduced left ventricular end diastolic volume and stroke volume [23]. In this study from Barr et al. on a very large cohort of normal subjects and patients with mild COPD, left ventricular dimensions were correlated to FEV_1. We speculate that this observation may be partially

explained by a sequence starting from airway obstruction leading to increased intrathoracic pressure, subsequent underfilling of the right ventricle and finally, underfilling of the left ventricle and a decrease in stroke volume. The possible role of fluid status and the use of diuretics on the observed relationship between FEV_1 and cardiac dimensions in the patients studied by Barr et al. was addressed in the correspondence which followed the original publication [5].

It is conceivable that the hemodynamic impairment in COPD can be described as a continuum between two extremes. On the one hand, there are patients with a low pulmonary artery pressure in whom a normal right atrial pressure translates into impaired right atrial filling and a low right ventricular output at the end of expiration. On the other hand, there are COPD patients with an elevated pulmonary artery pressure, who are functionally impaired by a high afterload but have a normal right ventricular preload. In these patients, stroke volume is impaired during the entire respiratory cycle, as the elevated right atrial pressure maintains a constant filling pressure of the right ventricle. The heterogeneity of the disease implies that individual COPD patients may have different combinations of preload and afterload impairments.
In conclusion, we here show that in COPD, the pulmonary artery pulse pressure declines during expiration, and that this effect is most prominent in patients with a low right atrial filling pressure. This implies that expiratory airflow limitation leads to expiratory blood flow limitation in the pulmonary circulation. Impaired right atrial filling during expiration may explain part of the impairment in resting and exercise stroke volume in COPD patients.

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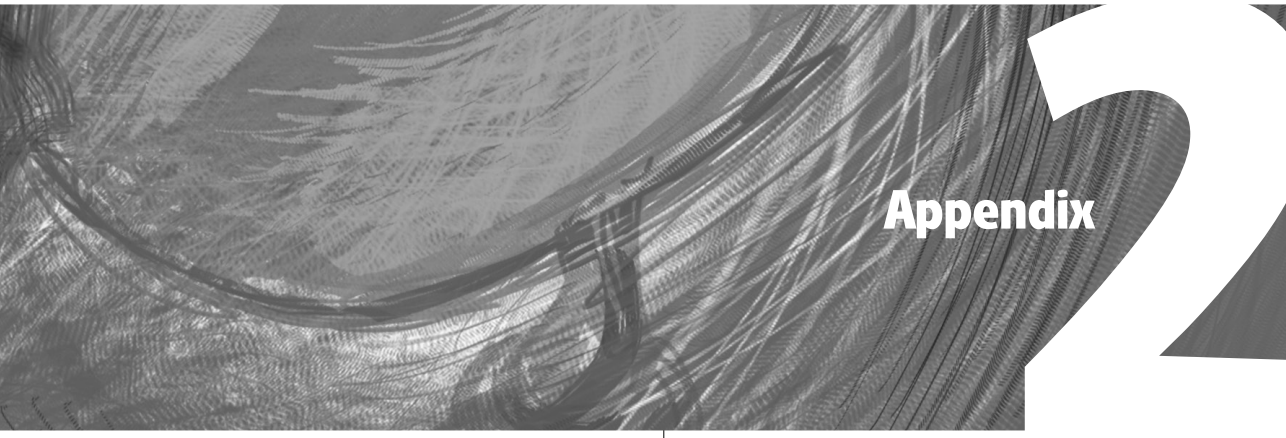
Spirometry in COPD: a hemodynamic rollercoaster?



Appendix

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Image in pulmonary medicine:
Am J Respir Crit Care Med. 2012 Aug 15;186(4):e6-7 2 .

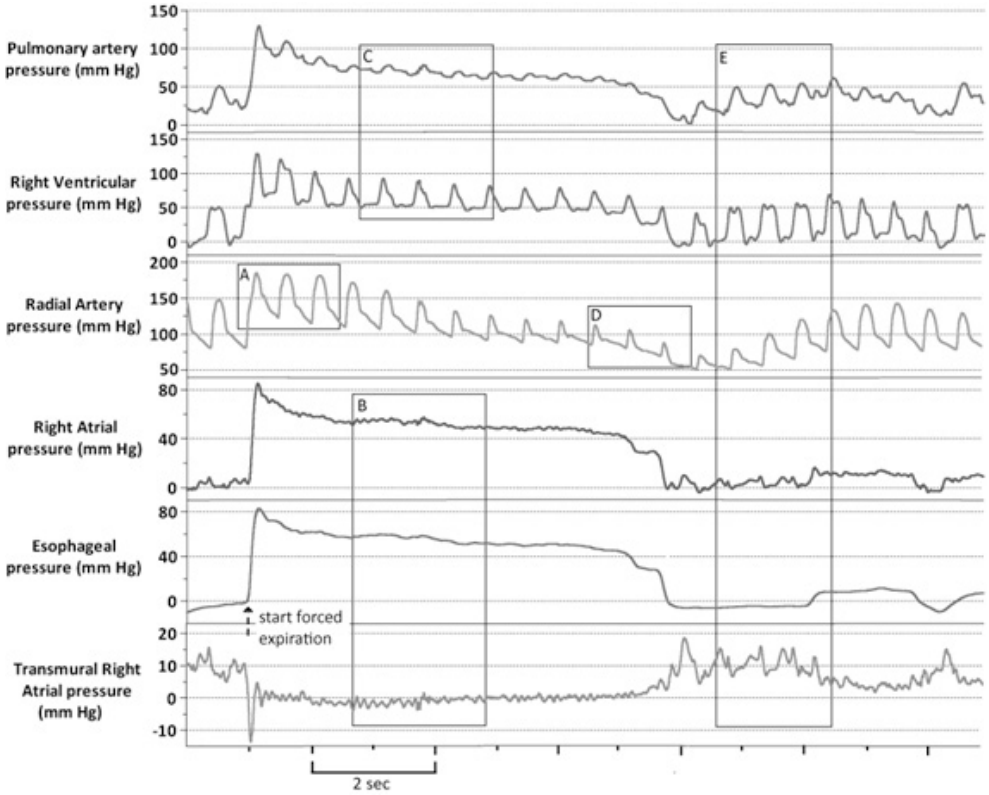

Figure 2a.1 *Simultaneous recording of pressures in (from top to bottom) the pulmonary artery, right ventricle, right atrium, radial artery, esophagus and the calculated transmural pressure of the right atrium (right atrial minus esophageal pressure) during a forced expiration in a patient with very severe COPD. See text for explanation of the panels.*

A 70-year old female patient with very severe COPD (FEV_1/SVC: 46%, FEV_1: 0,62 L, 29% of predicted). The patient gave informed and written consent to participate in a larger, institutional review board approved study of the effects of airflow limitation and hyperinflation on the central hemodynamics (Medical ethical review committee VU University Medical Center, registration number: NL30766.029.10). Some of the results of this study have been previously reported in the form of an abstract. (1). She performed a forced expiratory flow maneuver with simultaneous central hemodynamic measurements using a pulmonary artery catheter and measurement of pleural pressure using an esophageal balloon.
At the onset of the forced expiration, the increase in pleural pressure forces blood into the left heart leading to a (pulse) pressure increase in the radial artery (A). However, at the same time venous return is impaired indicated by the low transmural pressure of the right atrium (B). As a consequence right ventricular output decreases, reflected by a decrease in pulmonary artery pulse pressure (C). The decline in right ventricular output is followed by a decrease of left ventricular output leading to a marked decrease in (pulse) pressure in the radial artery (D). Overall, a drop in systemic blood pressure to 70/50 mmHg is the result of this forced expiration. With the first subsequent inspiration all values return to baseline (E).

Although for this very severe COPD-patient a forced expiratory maneuver in COPD acted as a valsalva-maneuver with large negative effects on cardiac function, she remained asymptomatic. The response of the radial artery pressure to the forced expiration looked very similar to the exaggerated response to a valsalva maneuver described in emphysema-patients, characterized by an marked diminution in pulse pressure, a delay in the return to baseline-values and an absent overshoot in pressure. (2) The resultant drop in systemic blood pressure supports the recommendation that spirometry should be performed in a sitting position. (3)

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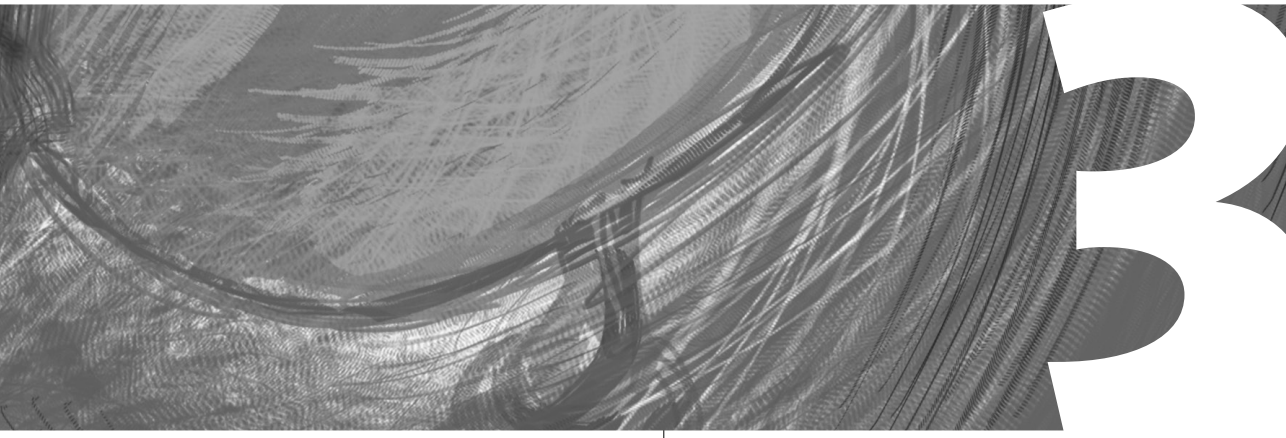
The effect of heliox on venous return and stroke volume in patients with chronic obstructive pulmonary disease.



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ABSTRACT

Background

In patients with chronic obstructive pulmonary disease(COPD). Altered pulmonary mechanics due to airway obstruction may hamper stroke volume by lowering venous return. If so, improving airflow limitation could lead to an improvement in stroke volume.

Methods

Pleural pressure, dynamic hyperinflation and central hemodynamics were simultaneously measured in patients with COPD at rest and during exercise, both in ambient air and while breathing a normoxic helium-oxygen mixture (heliox).

Results

Seventeen patients with COPD GOLD II-IV were included (FEV_1: 53 ± 17%, FEV_1/VC: 42±10%). Heliox-breathing lowered expiratory pleural pressure at rest (3.8±2.6 to 1.8±2.3 mmHg) and during exercise (8.2±3.6 to 6.1±3.3 mmHg), both $p<0.05$.
At rest we found improvements in cardiac output (6.1±1.4 to 6.6±1.1 L/min/m^2), stroke volume (80±22 to 87±19 ml/m^2) and mixed venous oxygen saturation (66±6 to 69±6%; all $p<0.05$). Heliox did not improve these parameters during iso-exercise.

Conclusion

The improvement in pulmonary mechanics by heliox-breathing augments venous return and stroke volume at rest in patients with moderate to very severe COPD. During exercise heliox-breathing did not affect stroke volume

INTRDUCTION

Patients with chronic obstructive pulmonary disease (COPD) are characterised by a low stroke volume at rest [1] and an impaired ability to increase stroke volume in response to exercise[2,3]. Established causes of an impaired cardiac function in COPD are pulmonary vascular disease [4] with right ventricular dysfunction [5] and occult left ventricular dysfunction [6]. In addition, there is a growing amount of literature suggesting a negative effect of airway obstruction on cardiac output [7,8]. The most likely mechanisms by which airway obstruction may impair the circulation are an increase in expiratory intrathoracic (or pleural) pressure [9,10] and a compressive effect of hyperinflated lungs on cardiovascular structures [11]. Subsequent disturbances in venous return [12,13] and impaired filling of the right and left ventricles [14,15] can lower stroke volume. If venous return and stroke volume are indeed adversely affected by an airway-obstruction related increase in expiratory pleural pressure, lowering expiratory pleural pressure by improving airflow should lead to a better stroke volume. A normoxic helium-oxygen mixture (heliox) is known to lower pleural pressures and hyperinflation in COPD [18,19]. Previous studies showed a positive effect of heliox on stroke volume and suggested that venous return improved. [7,8] However, venous return was not measured in these studies and stroke volume by non-invasive approach. The aim of this study to evaluate, in patients with COPD, the effect of lowering expiratory pleural pressure using heliox on right heart filling and stroke volume at rest and during exercise. Changes in central hemodynamics of patients with COPD were evaluated by right heart catheterisation at rest and during exercise, before and while breathing heliox.

METHODS

Patients

Between May 2010 and January 2012 patients were included with moderate to very-severe COPD. Exclusion criteria were a history of left-sided cardiac failure, left-ventricular dysfunction on Doppler-echocardiography, valvular disease, atrial fibrillation, an acute exacerbation of COPD within 4 weeks prior to inclusion or an inability to perform exercise. Additionally, patients with out-of-proportion pulmonary hypertension were excluded (mean pulmonary artery pressure; mPAP>40 mmHg). [16] The study had institutional review board approval. All patients were informed and gave written consent to the procedures. Data from the measurements in ambient air of all patients were also, in part, used in a previous study. [12]

Study Protocol

The study protocol consisted of three exercise tests on two consecutive days. On the first day patients performed an incremental cardio-pulmonary exercise test (CPET) using an electromagnetically braked cycle-ergometer (Ergoline GmbH, Bitz, Germany) in order to acquire maximal exercise tolerance. On the second day there were two identical rest-exercise tests (at an intensity of 50% of the previously estimated maximal workload) with hemodynamic measurements using pulmonary artery and radial artery catheters together with an esophageal balloon catheter. Details about the preparation of the subjects were described previously. [12]

Resting measurments were made after at least 3 minutes rest in semi-supine position. Exercise measurements with roomair and heliox at an identical timepoint at a similar

workload (isotime, isowork). The exercise protocol consisted of 3 minutes of rest after which the work rate was increased either directly to 50% of patients' maximal workload or via one additional step of three minutes, depending on the physical condition of the patient. The first test was always performed in roomair, for diagnostic purposes, and the second test with heliox. During the second test heliox was administered by a Douglas-bag attached via two one-way valves to the inspiratory site of a non-rebreathing system. Between the two tests patients were allowed to rest for at least 45 minutes, at least until the heart rate returned to below 105 % of the patients' resting heart rate.

Measurements

Breath-by-breath measurements were made of oxygen consumption (VO_2), ventilation (VE) using a metabolic chart (Vmax229, Sensormedics, Yorba Linda, CA, USA) in ambient air or a Triple-V (Erich Jaeger, Viasys Healthcare, Germany) when breathing heliox. Comparison of the two systems showed good agreement in measurements of VO_2 and IC. [17] Pressures in the pulmonary artery, right atrium, right ventricle, radial artery and esophagus were continuously recorded together with heart rate. For analyses, end-expiratory pressures were averaged over the last 30 seconds of each condition. After 3 minutes of rest and at the end of exercise, measurements were made of pulmonary capillary wedge pressure (PCWP) an Inspiratory Capacity (IC) together with sampling of arterial and mixed venous blood. Afterwards cardiac output (CO, direct-Fick-method), stroke volume (CO/heart rate) and pulmonary vascular resistance (PVR; 80*(mPAP-PCWP)/CO) were calculated. Transmural pressure of the right atrium (RAPtm), as a measure of right sided filling, was calculated as right atrial pressure minus oesophageal pressure at the end of expiration.

Statistical methods

Data is presented as mean ± standard deviation, unless stated otherwise. Differences between ambient air and heliox at rest and during exercise within patients were tested using a paired t-test with appropriate correction for multiple testing. $P<0.05$ was considered significant. Analyses were performed with GraphPad Prism 5.0. for Windows.

Results

Twenty-two consecutive patients were enrolled in this study. After the resting right heart catheterization, five patients were excluded for the heliox-trial: two patients because of a PWCP> 15 mmHg and three patients because of out-of-proportion pulmonary hypertension (mPAP>40 mmHg). As such, seventeen patients were eligible for inclusion. Demographic, lung function and hemodynamic characteristics are shown in table 3.1.

	Mean ± SD	% of pred
m/f	7/10	
Age (yrs)	68 ± 8	
Height (cm)	172 ± 7	
Weight (kg)	76 ± 14	
FEV_1 (L)	1.42 ± 0.54	53 ± 17
FEV_1/VC (%)	42 ± 10	
VC (L)	3.42 ± 1.1	99 ± 24
TLC (L)	6.46 ± 1.05	111 ± 17
FRC (L)	4.13 ± 1.05	140 ± 25
IC/TLC (%)	36 ± 11	
DLCO/VA	62 ± 19	
mPAP (mmHg)	24 ± 6	
CI ($L/min/m^2$)	3.2 ± 0.7	
HR (bpm)	77 ± 17	
PaO_2 (mmHg)	66 ± 14	
$PaCO_2$ (mmHg)	40 ± 7	

Table 3.1 ***Demographic, pulmonary function and hemodynamic characteristics.***
FEV_1: Forced expiratory volume in one second, VC: vital capacity, TLC: total lung capacity, functional residual capacity, IC: inspiratory capacity, mPAP: mean pulmonary artery pressure, CI: Cardiac Index, HR: Heart Rate, PaO_2: arterial oxygen tension, $PaCO_2$: arterial carbon dioxide tension.

According to the GOLD-criteria the severity of airflow obstruction was moderate in two patients, severe in thirteen patients and very severe in two patients. [18] The results of the CPET are summarized in table 3.2. Patients had, on average, a severely impaired exercise tolerance (VO_{2_max}: 57% of predicted). All patients showed a progressive decrease in IC (average ΔIC: 0.65 ± 0.39) during exercise and a marked decrease in arterial oxygen saturation from 92 ± 5% at rest to 85 ± 8 at maximal exercise.

Effect of heliox on ventilation and pulmonary mechanics

The effects of heliox on parameters of ventilation and pulmonary mechanics are summarized in table 3.2. Reliable measurements of ventilatory parameters (VE, f_B and VO_2) could not be acquired in two patients during heliox-breathing due to technical problems with the Triple-V sensor. No significant effect of heliox was found on VE, f_R and V_t in the other patients. In addition, heliox-breathing had no significant effects on inspiratory capacity at rest or on the decrease in inspiratory capacity during exercise ($P_{interaction} = 0.86$). End-epxiratory Peso decreased with heliox from 3.8±2.6 to 1.8±2.3 mmHg ($p<0.05$) at rest and from 8.2±3.6 to 6.1±3.3 mmHg during exercise (both $p<0.05$). See figure 3.1.

	Mean ± SD	% of pred
Peak workload (w)	58 ± 40	43 ± 24
Peak VO_2 (ml)	987 ± 425	57 ± 17
VO_{2_max}. ml/kg/min	13.0 ± 4.0	56 ± 17
VE_{peak}. L/min	38 ± 18	73 ± 19
HR_{max} (beats/min)	116 ± 19	
RER	1.00 ± 0.13	
pET_CO_2 rest	33 ± 6	
pET_CO_2 max	37 ±7	
VE/VCO_2 rest	48 ± 7	
VE/VCO_2 max	37 ± 8	
SpO_2 rest	92 ± 5%	
SpO_2 max	85 ± 8	
IC rust	2.36 ± 0.91	
IC max	1.71 ± 0.61	
Vt rest (L)	0.65 ± 0.15	
Vt max	1.14 ± 0.56	

Table 3.2 ***Results of the cardiopulmonary exercise test***
VO_2: Oxygen consumption, VE: Minute ventilation, HR: Heart Rate, RQ: Respiratory exchange ratio, pET_CO2: End-Tidal carbon dioxide pressure, VE/CO_2 ventilatory equivalent of carbon dioxide production. SpO_2: oxygen saturation, IC: inspiratory capacity, Vt: Tidal Volume, IRV: inspiratory reserve volume.

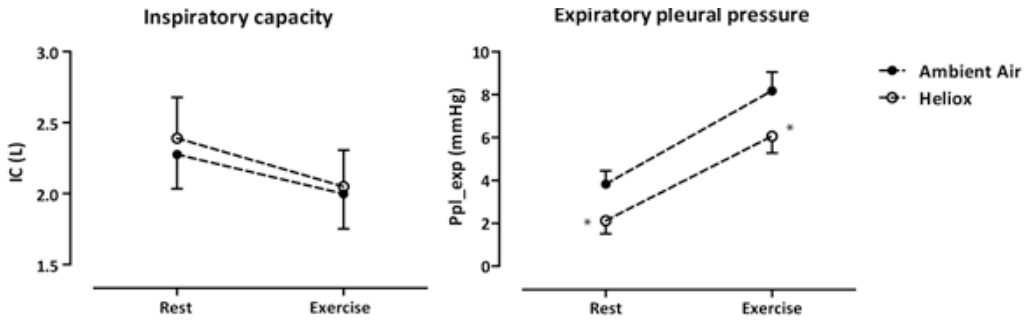

Figure 3.1 *Measurements of pulmonary mechanics in ambient air and during heliox breathing. IC: Inspiratory capacity, Peso_exp: end-expiratory pressure. Heliox did not change the IC at rest nor the amount of exercise induced dynamic hyperinflation. Heliox lowered pleural pressure during the entire exercise period. * p<0.05*

	Rest		Exercise	
	Ambient Air	Heliox	Ambient Air	Heliox
VE (L/min)	13.0 ± 3.5	11.1 ± 3.9	25.6 ± 8.5	23.9 ± 7.5
f_R (br/min)	19 ± 3	18 ± 5	27 ± 6	25 ± 9
Vt (L)	0.68 ± 0.18	0.62 ± 0.23	0.91 ± 0.43	1.06 ± 0.54
IC (L)	2.28 ± 0.87	2.39 ± 1.04	2.00 ± 0.89	2.05 ± 0.95
EELV (L)	3.98 ± 0.95	3.86 ± 0.97	4.25 ± 0.92	4.21 ± 0.94
$Peso_{exp}$ (mmHg)	3.8 ± 2.6	1.8 ± 2.3†	8.2 ± 3.6	6.1 ± 3.3†
$Peso_{exp\text{-}insp}$ (mmHg)	10.3 ± 3.4	8.7 ± 3.6 †	17.6 ± 4.6	16.4 ± 5
P_aO_2 (mmHg)	66 ± 14	64 ± 11	56 ± 16	52 ± 13
P_aCO_2 (mmHg)	40.1 ± 7.4	39.5 ± 7.9	41.8 ± 7.4	39.5 ± 7.9

Table 3.3 Effect of Heliox on pulmonary function, mechanics and gas exchange
VE: minute ventilation, fR: respiratory frequency, Vt: tidal volume, IC: inspiratory capacity, EELV: end-expiratory lung volume, Peso_exp: end-expiratory pleural pressure, Peso_exp-insp: pleural pressure swings (expiratory-inspiratory), PaCO2: arterial carbon dioxide tension. †: p<0.05 versus same condition in ambient air. VE, fR, Vt, IC and EELV were measured in 15 patients.

Effect of heliox on central hemodynamics

The effects of heliox on central hemodynamics and cardiac function are summarized in table 3.4 and figure 3.2. Because VO_2 could not be measured during heliox-breathing in two patients, the thermodilution-method was applied, instead of the Fick-method, to acquire cardiac output. At rest, heliox-breathing resulted in an increase in stroke volume (78±21 ml to 87±18 ml) and cardiac output (6.1±1.4 l/min to 6.6±1.5 l/min, p<0.05), which was accompanied by an increased mixed venous oxygen saturation (SvO_2; from 66±6 % to 69±6 %, p<0.05). During exercise, no significant effects were found of heliox on stroke volume (92±26% vs. 90±23%), cardiac output (9.1±2.4ml vs. 9.3±2.1ml), mixed venous oxygen saturation (44±8% vs. 42±7%), or oxygen tension or saturation. RAP_tm increased with heliox at rest as well as during exercise. No effects were found of heliox-breathing on pulmonary artery pressure

	Rest		Exercise	
	Ambient Air	Heliox	Ambient Air	Heliox
HR (bpm)	77 ± 17	79 ± 16	100 ± 13	104 ± 14
S_aO_2 (%)	92 ± 5	92 ±3	86 ± 9	84 ± 9
$S_{a\text{-}v}O_2$ (%)	26 ± 1	23 ± 5†	42 ± 8	42 ± 8
VO_2 (ml/min)	285 ± 68	296 ± 69	700 ± 227	728 ± 251
mPAP (mm Hg)	24 ± 6	25 ± 7	45 ± 13	43 ± 11
PCWP (mm Hg)	10 ± 2	9 ± 3	17 ± 10	15 ± 7
PVR (dyne/s/cm^5)	242 ± 113	209 ± 99†	248 ± 128	242 ± 79

Table 3.4 *HR: heart rate, SaO2: arterial oxygen saturation, Sa-vO2: arterial-venous oxygen difference, mPAP: mean pulmonary artery pressure, VO2: oxygen consumption, PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance. mRAP: mean right atrial pressure. †: p<0.05 versus same condition in ambient air. Measures of CI and SVI were bases on the fick-method in 15 patients and in 2 patients with thermodilution. VO2 was measured in 15 patients.*

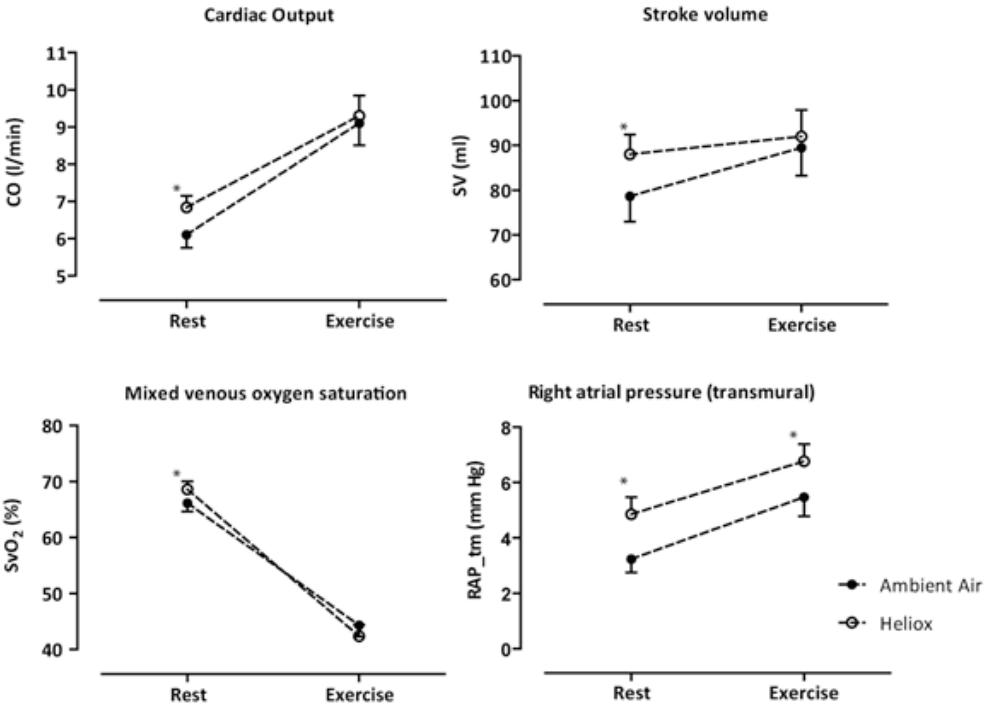

Figure 3.2 ***Measurements of cardiac function in ambient air and during heliox breathing.***
*CO: cardiac output, SV: Stroke Volume, SvO_2: mixed venous oxygen saturation. RAP_tm: transmural right atrial pressure. With heliox we found improvements in CO, SV and SvO_2 at rest. No improvements were found at identical intensity exercise. Rap_tm increased with heliox rest and exercise * p<0.0*

DISCUSSION

We investigated whether mitigating the disturbed pulmonary mechanics in COPD by breathing heliox would enhance stroke volume at rest and during exercise. This study is the first to evaluate the effects of heliox on pulmonary mechanics and stroke volume by carrying out simultaneous determinations of Peso, hyperinflation and (invasively measured) central hemodynamics. Pulmonary mechanics were indeed improved by heliox, as shown by the lowered expiratory Peso. Our main finding is that breathing heliox improved stroke volume and CO at rest, but not during exercise.

The improvements in stroke volume, cardiac output, and mixed venous oxygen saturation while breathing heliox suggest that airflow limitation has a negative effect on stroke volume at rest. Stroke volume improved with heliox in the presence of a lowered expiratory Peso while hyperinflation was not affected, implying that airflow limitation affects cardiac function by increasing expiratory Peso, rather than by direct effects of hyperinflation. The lowered Peso most likely improved venous return, which is known to be disturbed in COPD [7,13], as RAPtm increased. At rest, without the action of peripheral muscles, venous return depends on the interplay between central venous pressure and the intrathoracic (or pleural) pressure. A lower Peso translates into a larger pressure gradient for

blood entering the thorax during expiration, which leads to an increased cardiac output. It was shown in a large population based study, that stroke volume at rest is inversely related to the severity of airflow limitation [1]. While stroke volume at rest is only moderately reduced in COPD, mitigating airflow by heliox did result in a significant improvement. Therefore, airflow limitation and the accompanying altered pulmonary mechanics of breathing can contribute to a decreased stroke volume in COPD.
The absence of significant improvements in exercise stroke volume after heliox-breathing may have several explanations. With exercise in ambient there was an increase in RAP_tm compared to rest, indicating that venous return increased. With heliox at rest we found a similar increase in RAP_tm. The further increase in RAP_tm with heliox during exercise was not accompanied by an increase in SV. It is therefore possible that an increased Peso has negligible effects on venous return during exercise because exercising muscles provide for a sufficient venous return regardless of any elevations in Peso.[19] This is also suggested by the fact that in COPD, the slope of cardiac output to VO_2 during exercise is in general normal (3, 25).
We were not able to decrease (dynamic) hyperinflation with heliox. Dynamic hyperinflation is thought to have additional effects on the circulation. Hyperinflation might not only increase Peso, it is thought that it might increase the afterload of both ventricles [8,20,21]. which might also have caused the absence of improvement of stroke volume. The absence of improvement of exercise stroke volume might be causes by the unchanged lung hyperinflation after heliox. The stroke volume limitation could be caused rather by (modest) elevations in pulmonary artery pressure and PVR. [24,25], which could not be altered with heliox. Lastly, the lack of effect of heliox-breathing on exercise stroke volume could also be explained by the fact that the associated reduction in Peso was simply too small to improve stroke volume.

Our results are in line with a study of Oelberg et al. [22], who conducted the only other study to evaluate the central hemodynamics during heliox-breathing in COPD by means of invasive methods. They found no effect of heliox on cardiac output at peak exercise in eight patients with very severe COPD. Measurements were not performed at isotime and isowork in room air and heliox, as we have done, thereby precluding the separation of effects of heliox breathing on exercise tolerance versus effects on hemodynamics per se. Louvaris et al. recently tried to distinguish the effects of increased intrathoracic or gastric pressure and the effects of hyperinflation on the circulation. [8] They found that in patients who do not hyperinflate, heliox improved cardiac output, probably by enhancing venous return. In patients with dynamic hyperinflation, cardiac output did not improve with heliox. The authors suggest that the non-hyperinflators more strongly recruit expiratory muscles, especially in the abdominal region, which can depress venous return. This is in line with our finding increase in stroke volume at rest was due to a decrease in intrathoracic pressure, rather than by lowering hyperinflation. All but three patients showed dynamic hyperinflation, defined as a decrease in IC of more than 150 ml [8,23], which might be an alternative explanation that during exercise heliox did not improve stroke volume.

The importance of our study lies in the simultaneous measurements of hemodynamic variables and pulmonary mechanics, allowing for the first time to directly determine the interaction of the effects of heliox on pulmonary mechanics and cardiac function. Moreover,

the present study is unique because cardiac output was measured using gold-standard techniques and comparisons were made between hemodynamics measured in ambient air and during heliox breathing at identical exercise intensities.
Heliox has been shown to increase exercise endurance [6,18,19], which is accompanied by improvements in ventilatory capacity and dynamic hyperinflation according to some investigators [24,25], whereas others found no improvements in hyperinflation by heliox. [26,27] In our study, heliox had no effects on hyperinflation at rest or operating lung volumes during exercise. It has been suggested that the conflicting findings in the different heliox studies may be explained by varied inclusion of so called hyperinflators and non-hyperinflators.[28,29]
Most studies agree that heliox relieves the sensation of dyspnea and enhances exercise tolerance. It has become increasingly clear that exercise induced dyspnea in COPD arises from critical constraints on tidal volume, facilitated but not directly caused by dynamic hyperinflation. [28,29] Through an absent effect of heliox on cardiac output during exercise, our study confirms that the improved exercise capacity with heliox is explained by improved ventilatory mechanics and a relief of dyspnea [25,30,31,32], rather than by an effect on the circulation. This conclusion is in line with the idea that in the majority of the COPD-patients, exercise capacity is limited by a reduced ventilatory capacity. [33]

Our study has some limitations. Measurements were performed during submaximal exercise because the patients had to continue the exercise for at least 3 minutes. Because stroke volume is known to reach (near)-maximal values after about 40% of maximal exercise tolerance, we deemed steady state exercise at 50% of maximal exercise tolerance sufficient. Moreover, the purpose of the study was to investigated hemodynamic differences at isotime and not to study whether heliox would enhance exercise capacity. We did not randomize the order of testing in ambient air and heliox. The large resting period in between tests, with a demonstrated normalization of heart rate and $VO_{2,}$ argues against the introduction of a significant bias.

In conclusion, this study shows that in COPD, lowering expiratory pleural pressure with heliox improves stroke volume and cardiac output at rest. Modest improvements in pulmonary mechanics with heliox-breathing during exercise do not affect exercise stroke volume.

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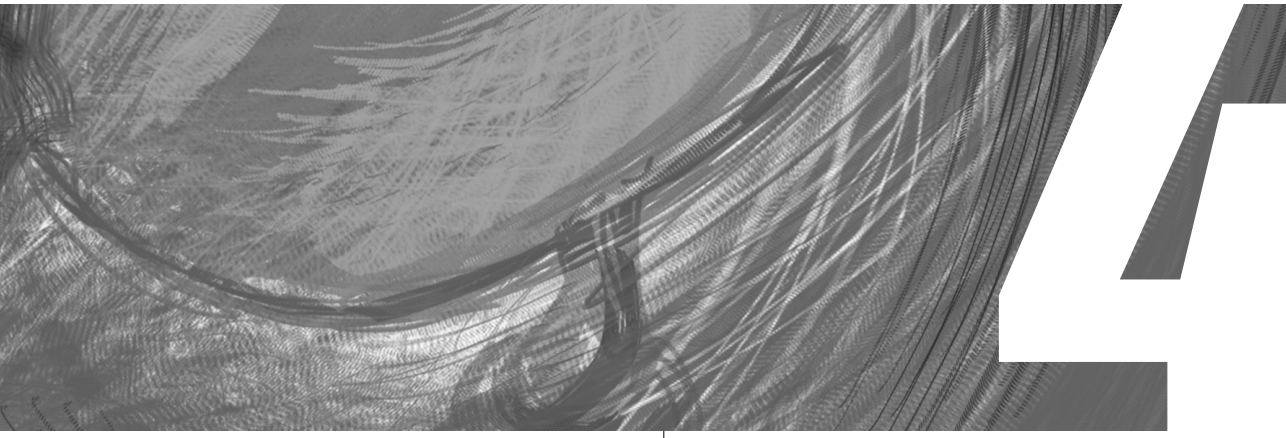
Central vascular pressure measurements during exercise in COPD: how to handle the respirophasic changes?



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ABSTRACT

Introduction

Respirophasic changes are a major confounder when evaluating central hemodynamics during exercise. We studied the accuracy of four different methods to assess mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) in case of heavy respiratory swings.

Methods

Central hemodynamics were measured simultaneously with esophageal pressure during maximal exercise in 30 patients with chronic obstructive pulmonary disease, known to develop excessive respirophasic swings. mPAP and PCWP were assessed at end-expiration, averaged over the respiratory cycle and corrected with a from the right atrial pressure (RAP) waveform estimated intrathoracic pressure an compared with the transmural pressures. The respiratory swings in mPAP, PCWP and RAP were compared.

Results

Measuring at end-expiration resulted in an overestimation of the intravascular pressure. Bland-Altman analyses showed the best agreement of mPAP averaged over the respiratory cycle (bias:2.5 mmHg , limits of agreement: -6.0 to 11.8) and when corrected with the nadir of RAP (bias: -3.6 mmHg , limits of agreement: -11.2 to 3.9). Measuring mPAP at end-expiration (bias: 10.3 mmHg , limits of agreement: 0.5 to 20.3) and mPAP corrected with the swing in RAP (bias: -9.3 mmHg , limits of agreement: -19.8 to 2.1) resulted in lower levels of agreement. The respiratory swings in mPAP and PCWP were similar (r^2 = 0.82, slope: 0.95 ± 0.1)

Conclusion

Central hemodynamics measured at end-expiration leads to an overestimation of intravascular pressures in exercising COPD-patients. Averaging pressures over the respiratory cycle or using the right atrial pressure waveform to estimate and correct for intrathoracic pressure leads to better estimations of intravascular pressure. The assessment of the pulmonary gradient is unaffected by respiratory swings.

INTRODUCTION

Hemodynamic assessment remains the gold standard in the diagnosis of cardiovascular and pulmonary vascular disease. Co-morbidities, particularly those that alter pulmonary mechanics can make interpretation of both resting and exercise hemodynamics difficult. In an effort to detect early and potentially more treatable pulmonary vascular disease [1,2], and heart failure with preserved ejection fraction (HFpEF)[3], there has been renewed interest in the direct measurement of central hemodynamics during exercise. Respirophasic swings are one of the major confounders when measuring exercise hemodynamics. The end of an expiration is the moment in the respiratory cycle at which the pressure inside the thorax (intrathoracic pressure, ITP) is closest to atmospheric pressure at rest [5]. To minimize the contribution of ITP to intravascular pressure measurements during a right heart catheterization, it's recommended to analyse pressures at end expiration [6]. With exercise, significant respirophasic swings in ITP and a rise in ITP at end-expiration can develop. The high end-expiratory ITP occurs in patients with chronic obstructive lung disease (COPD) due to increased lung compliance and auto-PEEP [7,8], but can also be present in the normal elderly population due to recruitment of expiratory muscles during exercise [9]. When central pressures are measured during a period of positive ITP this might lead to overestimation of the true intra-cavitary or transmural pressure, which are critical in the detection of pulmonary vascular disease. Subtracting esophageal pressure (P_{eso}) is preferable [10], however not practical in most studies. Older studies therefore reported the values of central pressures averaged over one or more respiratory cycles with exercise in COPD[11,12,13] and healthy subjects[14,15,16]. More recent studies abandoned this and switched to end-expiratory measurements [17,18], based on the recommendations for resting measurements under the assumption that they also hold during exercise. An alternative is to use the right atrial pressure (RAP) waveform, which is largely influenced by its surrounding pressure, to estimate ITP [19]. How to measure central pressures with exercise in case of exaggerated ITP swings and the validity of using the RAP-waveform to correct for ITP remain largely unknown. In this study we therefore evaluated the effect of ITP on the different central pressures in patients with COPD. We hypothesized that measuring at end-expiration leads to an overestimation of pulmonary vascular disease and that averaging over the respiratory cycle or correcting the pulmonary artery pressure with an estimated intrathoracic pressure results in better assessment of the intravascular pressure. Secondly, we hypothesize that the respiratory swings with exercise in pulmonary artery pressure and wedge pressure are similar, so that the transpulmonary gradient can be assessed unaffected by respiratory swings.

METHODS

Subjects

COPD Patients (n=30) were referred for the analysis of pulmonary hypertension. Patients were selected based on a moderate to very severe airway obstruction (forced expiratory flow in 1 second, FEV_1<80% of predicted), without significant reversibility (<12% or <200 ml change of the FEV_1 value). All patients were on optimal medical therapy for their COPD and had not had an acute exacerbation for at least 4 weeks. Full pulmonary function testing was performed according to published guidelines. [20,21]. All tests were performed in the VU university medical centre and the VU university medical centre ethics committee approved the study. Written informed consent was obtained from all patients.

Subject preparation

All subjects underwent pulmonary artery, and radial artery catheterization, and placement of an esophageal balloon catheter. A balloon tipped, flow directed, triple lumen 7.5F Swan-Ganz catheter (Baxter HealthcareCorp; Irvine, CA), was inserted under local anaesthesia in the jugular vein. The ports of the catheter were positioned in the right atrium, right ventricle and pulmonary artery. A radial artery catheter was inserted at either the right or left wrist under sterile conditions and following local anesthesia. A standard esophageal balloon-catheter (Microtek Medical B.V. Zutphen, The Netherlands) was inserted trans-nasaly with the use of lidocaine gel (2%). The balloon tip was first positioned 45 cm from the nares after and the balloon was emptied by performing a Valsalva maneuver. [22] Five mL of air was injected into the balloon followed by the withdrawal of 4 mL to partially inflate the balloon. The pressure signal was checked and in case of cardiac artefacts the position of the balloon-catheter was slightly adjusted in proximal direction.

Patients were placed on an electromagnetically braked cycle ergometer (Ergoline GmbH, Bitz, Germany), in semi-supine position. The zero reference for the pressure transducers was 5 cm below the middle of the sternum. All catheters were connected to a PowerLab data acquisition system (ADInstruments), in order to record and digitalize pressures from the right atrium, right ventricle, and pulmonary artery simultaneously with P_{eso}.

Protocol

The protocol consisted of three minutes of rest after which workload was increased every three minutes until exhaustion. Oxygen consumption (VO2) was measured continuously using a metabolic cart (Vmax 229, Viasys, Yorba Linda, CA, USA). Patients were asked to signal just prior to exhaustion in case the last workload could not be fulfilled for three minutes to complete the data collection at maximal exercise. During the last 30 seconds of every workload pulmonary capillary wedge pressure (PCWP) was acquired and mixed venous, and arterial blood samples were drawn. Cardiac output (CO) was calculated using the direct Fick-method from arterial- and mixed venous oxygen saturation (SaO_2, SvO_2) and VO_2. Pulmonary vascular resistance (PVR) was calculated as (mPAP - PCWP)/CO.

Post-processing of pressure waveforms

See online supplement for a more detailed description. By using a home-build program for Matlab (The MathWorks, Natick, MA) we automatically acquired systolic (sPAP), mean (mPAP), diastolic (dPAP) together with the transmural values of mPAP ($mPAP_{tm}$) and PCPW (PCWPtm) in a beat-to-beat manner. Transmural values were calculated by subtracting P_{eso} from the absolute values of mPAP and PCWP. See figure 4.1 one for an example of the PAP tracing before and after continuous correction for P_{eso}. All values were acquired and averaged over a period of 10-20 inspiratory and 10-20 expiratory heartbeats. This way we acquired robust inspiratory and expiratory values separately as well as the swings (expiratory-inspiratory values). In the same timeframe we acquired the nadir of RAP during expiration (RAP_{nadir}) and the respiratory swing in RAP (RAP_{swing}). See figure 4.2 for an example of determination of RAP_{nadir} and RAP_{swing}. We calculated the averaged values of mPAP ($mPAP_{averaged}$) and PCWP ($PCWP_{averaged}$) over at least three full respiratory cycles.

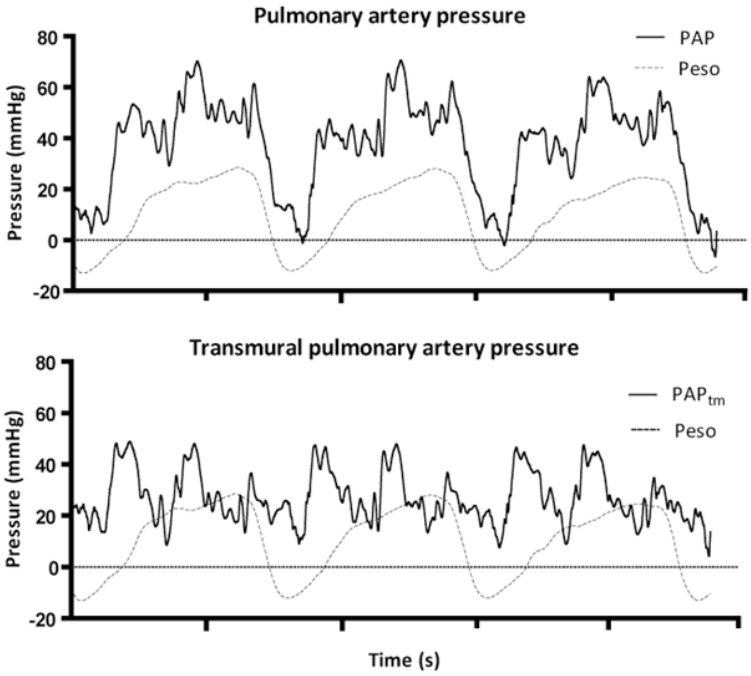

Figure 4.1 *Example of pulmonary artery pressure before (PAP) and after (PAP_{tm}) continuous correction for esophageal pressure (P_{eso}) at maximal exercise in a patient with severe COPD (FEV1: 30% of predicted).*

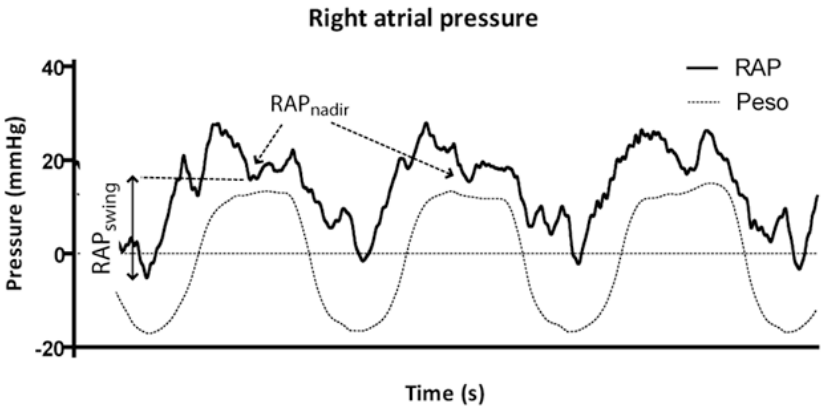

Figure 4.2 *Example of determinations of right atrial pressures (RAP).Shown are the simultaneous measurement of RAP and esophageal pressure (P_{eso}) at maximal exercise in a patient with severe COPD (FEV_1: 41% of predicted). RAP_{nadir} is the lowest point in RAP during expiration, which represents RAP during relaxation. Note that RAP falls towards P_{eso} during relaxation. RAP_{swing} was determined as the difference between inspiratory RAP and expiratory RAP.*

Analyses

We analysed the bias introduced by measuring mPAP and PCWP at end-expiration without correction for P_{eso} ($mPAP_{end\text{-}exp,}$ $PCWP_{end\text{-}exp}$). The increase in mPAP was interpreted as a function of the increase in blood flow with exercise ($mPAP_{end\text{-}exp}$/CO) and compared with the increase of $mPAP_{tm}$ increase with increase in blood flow ($mPAP_{tm}$/CO). The same was done for PCWP and $PCWP_{tm}$. An abnormal response of mPAP to exercise was defined as ΔmPAP/ΔCO>3 mmHg/L. For PCWP a threshold of 20 mmHg with exercise was used as an abnormal response of PCWP to exercise.

Secondly we compared different methods of measurements of mPAP and PCWP. $mPAP_{t\text{-}m}$and $PCWP_{tm}$during expiration were used as gold-standard for pulmonary artery pressures. We compared four different methods of correction for mPAPtm: 1) $mPAP_{end\text{-}exp}$2) $mPAP_{averaged}$, 3) end-expiratory mPAP corrected with RAP_{nadir}($mPAP_{rap\text{-}nadir}$)[19]and 4) end-expiratory mPAP corrected with RAP_{swing}($mPAP_{rap\text{-}swing}$). The same four methods were applied to PCWP.

We compared the $mPAP_{swing}$ with $PCWP_{swing}$and RAP_{swing} with $PCWP_{swing..}$ If the swing in mPAP and PCWP is similar this implicates that the transpulmonary gradient (mPAP-PCWP) and thereby PVR are unaffected by any swing in ITP. When the the swings in RAP and PCWP are similar, the increase in PCWP with exercise can be corrected for the increase in RAP with exercise (ΔPCWP/ΔRAP) [23] that could serve as a measure of PCWP with exercise that is unaffected by IP swings"

Statistical methods

Demographic, pulmonary function, and hemodynamic data are presented as mean ± standard deviation (SD). Differences in the slope and absolute values at rest and exercise before and after correction were tested using a 2-way ANOVA. The accuracy of the four different methods of measurements of mPAP and PCWP was evaluated by Bland-Altman analyses with $mPAP_{tm}$ and $PCWP_{tm}$ as gold-standard. The relations between $PCWP_{swing}$ and $mPAP_{swing}$ and betweenRAP_{swing} and $PCWP_{swing}$ were analysed by linear regression. Differences between $PCWP_{swing}$ and $mPAP_{swing}$ and between RAP_{swing} and $PCWP_{swing}$ were tested using a two-tailed student t-test. A P-value of <0.05 was considered significant. Analyses were performed using SPSS 15.0 or GraphPad Prism 5.0. for Windows.

RESULTS

	Mean ± SD	% of pred
FEV_1 (L)	1.58 ± 0.62	56 ± 18
FEV_1/VC (%)	46 ± 18	
VC (L)	3.46 ± 1.09	98 ± 22
TLC (L)	6.54 ± 1.20	109 ± 17
FRC (L)	4.19 ± 1.02	136 ± 34
CI ($L/min/m^2$)	3.3 ± 0.9	
HR (bpm)	80 ± 17	
PaO_2 (mmHg)	65 ± 15	
$PaCO_2$ (mmHg)	39 ± 9	

Table 4.1 ***Pulmonary function and hemodynamic characteristics***
FEV_1= forced expiratory flow in 1 second, VC = vital capacity, TLC= total lung capacity, FRC= functional residual capacity, CI= cardiac index, HR= heart rate, PaO_2= arterial oxygen tension, $PaCO_2$= arterial carbon dioxide tension.

Study Population

Fourteen men and sixteen women were included in this study with a mean age of 64 ± 9 years and a body mass index of 27 ± 6. Pulmonary function and hemodynamic measurements are summarized in table 4.1. Twenty-five patients were former smokers and 5 were current smokers (mean 37 ± 18 pack years), and had been diagnosed with emphysema based on pulmonary function and Computed Tomographic scanning of the chest. The severity of the airflow limitation was moderate in 16, severe in 11 and very severe in 3 patients according to the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria. Nine patients were hypoxemic (PaO_2<60 mmHg) at rest while breathing room air and four patients had a $PaCO_2$>45 mmHg.

Pressures during exercise with and without correction for ITP

Maximal exercise was at a workload of 48 ± 31 Watt with a VO_2 of 922 ± 379 ml. On average a CO of 10.9± 3.8 L/min was reached with a heart rate of 118 ± 19. The central hemodynamic pressures are summarized in table 4.2.

	Rest			Exercise		
	Expiration	Inspiration	Swing	Expiration	Inspiration	Swing
P_{eso} (mmHg)	3 ± 2	-7 ± 1	10 ± 3	12 ± 6	-11 ± 2	22 ± 6
sPAP (mmHg)	53 ± 20	45 ± 19	8 ± 6	87 ± 24	64 ± 21	22 ± 11
mPAP (mmHg)	33 ± 12	28 ± 11	6 ± 6	59 ± 14	40 ± 13	19 ± 8
dPAP (mmHg)	23 ± 9	15 ± 7	8± 5	40 ± 11	23 ± 11	19 ± 11
PCWP (mmHg)	11 ± 4	2 ± 4	9 ± 4	26 ± 8	5 ± 9	21 ± 6
mRAP (mmHg)	6 ± 2	-2 ± 3	7 ± 4	16 ± 6	-4 ± -4	20 ± 6

Table 4.2 ***Central pressure over the respiratory cycle at rest and during exercise.***
P_{eso} = esophageal pressure, sPAP, mPAP, dPAP = systolic, mean and diastolic pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, mRAP = mean right atrial pressure.

The large swings in P_{eso} were transduced into all central pressure; on average responsible for a difference between inspiratory values and expiratory values of about 20 mm Hg. The expiratory P_{eso} at maximal exercise ranged from+3 to+25 mmHg (Figure 4.3). The average slope decreased from 6.4 ± 3.7 to 4.4 ± 3.2 mmHg/L (p<0.001) after correction for ITP. Seven patients had a mPAP/Q slope >3 mmHg before correction which decreased to <3 mmHg after correction for the ITP. Twenty-two patients had a PCWP recording. Nineteen patients of the twenty-two had a PCWP>20 mmHg with exercise without correction for ITP. Seven patients a had $PCPW_{tm}$>20; in three of them $PCPW_{tm}$ was between 20 and 25 mmHg.

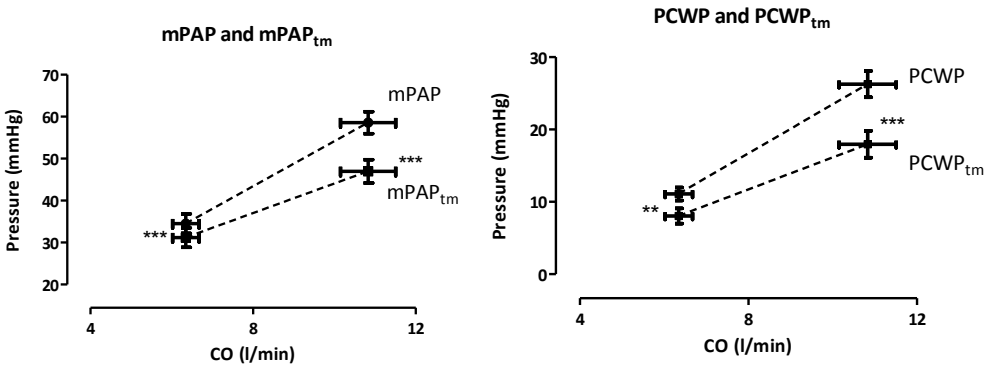

Figure 4.3 ***Average pressure flow relations before and after correction for esophageal pressure.***
*mPAP=mean pulmonary artery pressure, $mPAP_{tm}$= transmural mPAP (calculated as mPAP-P_{eso}) PCWP= pulmonary capillary wedge pressure. $PCWP_{tm}$=transmural PCWP (calculated as PCWP-P_{eso}). ** = p<0.01, ***=p>0.001.*

mPAP measurement and potential correction methods

$mPAP_{tm}$ and $PCWP_{tm}$ at maximal exercise were 47±15 and 17±8 mmHg respectively. The average mPAP values at maximal exercise of the four methods were; $mPAP_{end\text{-}exp}$: 59±14, $mPAP_{averaged}$: 50±14, $mPAP_{rap\text{-}nadir}$: 44±15 and $mPAP_{rap\_swing}$: 38±15 mm Hg. The average PCWP values at maximal exercise of the four methods were; $PCWP_{end\text{-}exp}$: 27±9, $PCWP_{averaged}$: 20±8, $PCWP_{rap\text{-}nadir}$: 15±7 and $PCWP_{\_swing}$: 11±8 mmHg. Bland-Altman plots of the four methods of mPAP and PCWP measurements during exercise are shown in figures 4.4 and 4.5 and summarized in table 4.3.

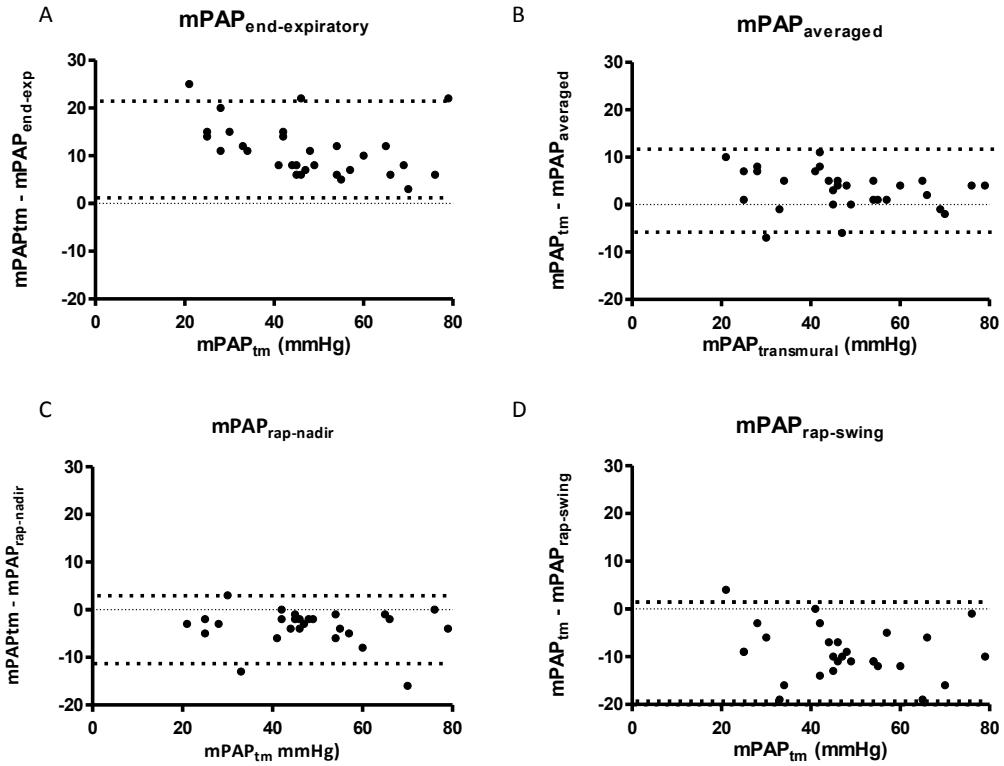

Figure 4.4 *Bland-Altman analyses of the difference between pulmonary artery pressure (mPAP) andtransmural mean pulmonary artery pressure ($mPAP_{tm}$)plotted versus the $mPAP_{tm}$. A) mPAP measured at end expiration, B) mPAP averaged over the respiratory cycle C) mPAP corrected with the lowest point of RAP during expiration (RAP-nadir) and D) mPAP corrected with the swing in RAP (RAP-swing). Dotted lines represent the 95% coincidence intervals.*

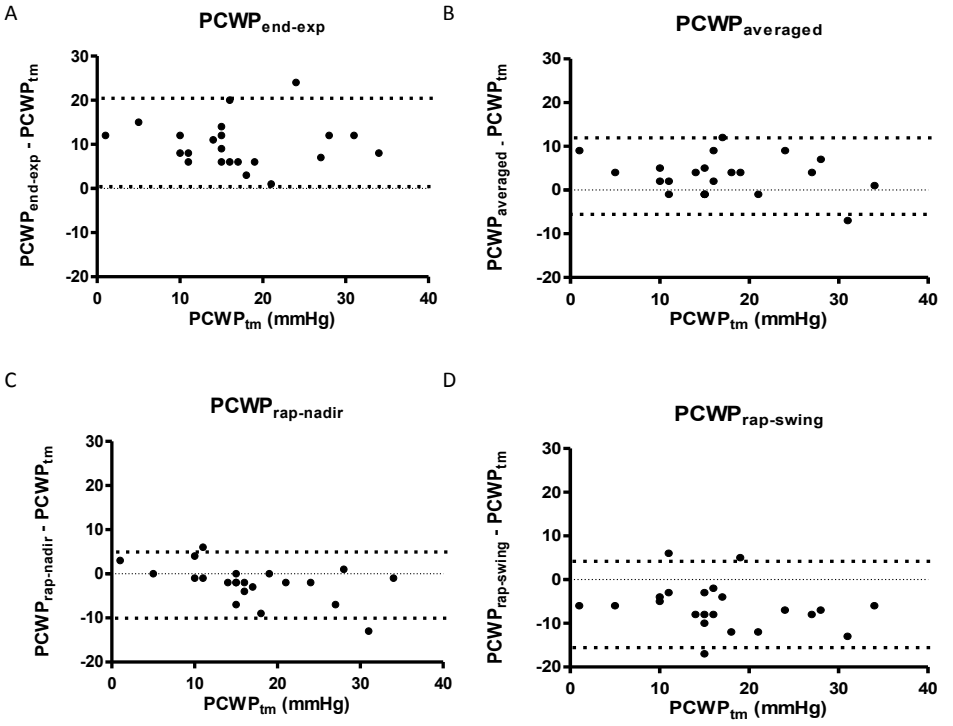

Figure 4.5 *Bland-Altman analyses of the difference between pulmonary capillary wedge pressure (PCWP) and transmural pulmonary capillary wedge pressure ($PCWP_{tm}$)plotted versus the $PCWP_{tm}$. A) PCWP measured at end expiration, B) PCWP averaged over the respiratory cycle C) PCWP corrected with the lowest point of RAP during expiration (RAP-nadir) and D) PCWP corrected with the swing in RAP (RAP-swing). Dotted lines represent the 95% coincidence intervals.*

Effect of ITP swings on PCWP, mPAP and RAP

See table 4.2 for a summary of the pressure fluctuations. Figure 4.6 illustrates the relation between $mPAP_{swing}$ and $PWCP_{swing}$. The swing in mPAP and PCWP did not differ (mean difference 0.9 mmHg, p=0.35). There was a strict relation between RAP_{swing} and $PCWP_{swing}$ (r^2=0.9, p<0.001) with a slope 1.02 and no significant difference between RAP_{swing} and $PCWP_{swing}$(mean difference 0.7 mmHg, p=0.28).

				95% limits of agreement (mmHg)	
	number	r^2	Bias ± SD (mm Hg)	From	To
$mPAP_{end\ expiratory}$	30	0.86	10.3 ± 5.9	0.5	20.3
$mPAP_{averaged}$	30	0.92	2.5 ± 4.4	-6.0	11.8
$mPAP_{rap\_nadir}$	30	0.94	-3.6 ± 3.8	-11.2	3.9
$mPAP_{rap\_swing}$	30	0.86	-9.3 ± 5.9	-19.8	2.1
$PCWP_{end\ expiratory}$	22	0.69	9.9 ± 5.3	-0.5	20.3
$PCWP_{averaged}$	22	0.75	3.2 ± 4.4	-5.3	11.8
$PCWP_{rap\_nadir}$	22	0.73	-2.0 ± 4.2	-2.0	4.2
$PCWP_{rap\_swing}$	22	0.64	-6.3 ± 5.3	-16.6	4.0

Table 4.3 ***Summary of Bland-Altman Analyses performed.***
mPAP=mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure

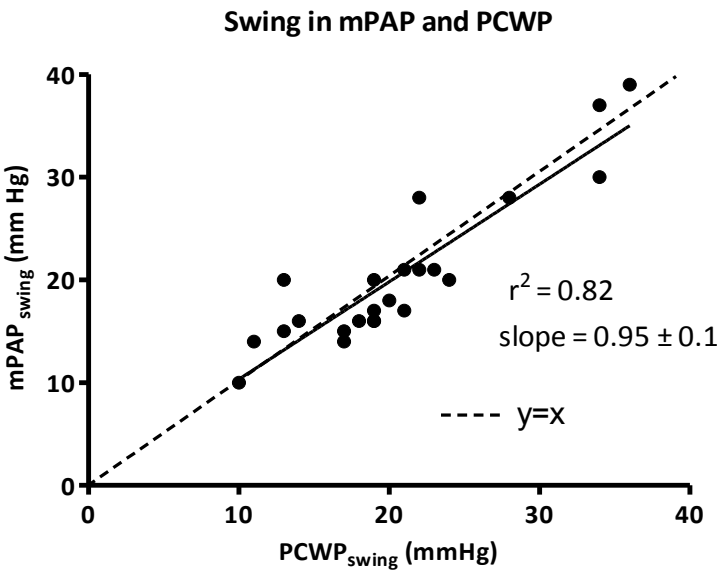

Figure 4.6 *The relation between the swing in mean pulmonary artery pressure ($mPAP_{swing}$) and the swing in pulmonary capillary wedge pressure ($PCWP_{swing}$).*

DISCUSSION

Errors due to respiratory variation are a major concern when interpreting central vascular pressures during exercise, especially in patients with airflow limitation. The aim of this study was to evaluate the potential error introduced in mPAP by measuring at end-expiration in only and to evaluate potential correction methods. We found that: 1) A significant error is introduced when mPAP and PCWP are measured during end-expiration in exercising COPD-patients, due to increases in expiratory ITP and that 2) averaging mPAP and PCWP over the respiratory cycle are better estimates of $mPAP_{tm}$ and $PCWP_{tm.}$ 3) The right atrial waveform can be used to correct for ITP in patients without right heart failure. 4) The transpulmonary pressure gradient (mPAP-PCWP), and thus pulmonary vascular resistance, is unaffected by ITP swings.

Our findings support the use of mPAP and PCWP averaged over 2-3 respiratory cycles in order to acquire more accurate assessment of the transmural values of mPAP and PCWP during exercise in COPD-patients. The patients in the present study showed a wide range of expiratory P_{eso} at exercise, reaching to as high as 25 mmHg, which is consistent with previous studies on pulmonary mechanics [7,8]. In these studies, as well as the present study, the positive excursion of P_{eso} during expiration is at least as large as the negative excursion during inspiration. It is therefore not surprising that mPAP averaged over the respiratory cycle is a more realistic measure of intravascular pressure. Albeit more accurate than $mPAP_{end\text{-}exp,}$ $mPAP_{averaged}$ was still a slight overestimation, which can be explained by the increased expiratory time. In COPD-patients expiratory time during exercise is longer than inspiratory time[24]. As a consequence, $mPAP_{averaged}$ is more influenced by the "high" expiratory mPAP than by the "low" inspiratory mPAP.

The usefulness of the RAP waveform to estimate the pressure surrounding the heart was shown by Tyberg et al. [19]. This method assumes that pressure in the very compliant right atrium is predominantly dependent on pressure surrounding the heart (pericardial pressure, or in our case ITP), rather than by right atrial volume. We showed that this method was useful during exercise in COPD-patients, as long as the lowest point of the RAP during expiration was used. This is explained by the fact that during the right atrial contraction dissociation between RAP and ITP is created. Therefore, only the pressure of an empty and relaxing right atrium is useful to estimate ITP. We found a small bias with $mPAP_{tm}$ and $PCWP_{tm}$ when RAP_{nadir} was used to correct expiratory mPAP and PCWP, with a very reasonable 95% CI. The small overcorrection in all patients is because it is unlikely that RAP_{nadir} can be lower than ITP at the same moment. This method may not be useful in patients with more pronounced right heart failure, as this causes RAP to rise, even during relaxation. Despite that, the average mPAP at rest in our cohort of COPD-patients is higher than normally reported in COPD [18,25], only 2 patients showed a RAP_{nadir} higher than ITP during exercise. We previously showed that some patients with COPD have an impaired venous return due to the high expiratory ITP, which makes that RAP_{nadir} is even closer to ITP. We further showed that the RAP_{swing} to estimated expiratory ITP was not useful in our patients. As RAP during inspiration can reach significant negative values, the total swing is larger than the positive excursion of ITP with expiration. Correction of mPAP with RAP_{swing} therefore lead to an underestimation of $mPAP_{tm}$.

Lastly, we showed that the swings in mPAP, PCWP and RAP were similar. This has several convenient implications. The consequence of an identical effect of ITP swing on mPAP and PCWP is that the difference between the two, the transpulmonary pressure gradient

is unaffected by the swing in ITP. This only holds when both the mPAP and PCWP being recorded at the same time point in the respiratory cycle. So, although individually, mPAP and PCWP are overestimations of intravascular pressure, the $mPAP_{end\text{-}exp}$ and $PCWP_{end\text{-}exp}$ combined lead to the correct transpulmonary pressure gradient or PVR (transpulmonary gradient/CO). It underscores the importance of PVR as part of the suggested definition of exercise induced pulmonary arterial hypertension [2], as it prevents patients being diagnosed simply because of an increased ITP. The similar rise in mPAP and PCWP from inspiration to expiration is consistent with the high ITP, per se, not contributing to right ventricular afterload, which is in agreement with previous literature on the effect of positive end expiratory pressure on right ventricular afterload. [26,27]

The similar effect of ITP swings in RAP and PCWP also has a potential implication in evaluating exercise hemodynamics. The increase in PCWP calculated as a ratio to the increase in RAP (ΔPCWP/ΔRAP), as previously suggested [23], is unaffected by ITP swings. This ratio might therefore be of potential help in the difficult situation of a high PCWP with exercise in the presence of ITP-swings; a situation that is common in COPD-patients. This would be especially helpful in diagnosing exercise-induced HFpEF. [3]

The patients in the presents study had at least moderate airflow limitation, likely a worst-case scenario for the influence of ITP on central pressure measurements. We can only speculated to what extent our findings can be extrapolated to patients with less severe airflow limitation or the normal elderly population. The positive expiratory ITP in COPD is mainly due to the use of expiratory muscles, not well related to the airflow limitation and the pattern of expiratory muscle recruitment differs between patients [28]. In the elderly population the use of expiratory muscles can lead to substantial positive ITP as well, albeit only at maximal exercise[9]. Pulmonary vascular pressure therefore should be averaged over 2 to 3 respiratory cycles not only in COPD [10,11,29] but also healthy subjects [14,15,16]. Whether an averaged mPAP is a more accurate estimate of the intravascular pressure at maximal exercise in this population remains unknown and depends on the amplitude and the length of the inspiratory and expiratory excursions in ITP. What is clear is that respiratory variation in central hemodynamic pressures during maximal exercise are not only present in severe COPD.

Limitations of this study warrant discussion. The average mPAP at rest in our cohort of COPD-patients is higher than normally reported in COPD due a referral bias, as our hospital is a pulmonary hypertension center. Therefore no conclusion should be drawn with regards to the incidence and severity of pulmonary hypertension at rest or during exercise in COPD from this study. We felt it was justified to use mPAP and PCWP after subtracting of P_{eso} as gold-standard, although small errors might be present in the measurement of P_{eso}. This was the only method in which ITP was taken into account when evaluating mPAP and PCWP and therefore the best way to answer our question.

In conclusion the present studies shows that substantial errors are introduced in interpretation of the absolute values of mPAP and PCWP during exercise in COPD when read only at end expiration. In order to acquire more accurate values, averaging over the respiratory cycle or correction with the estimated ITP from the RAP waveform should be performed. The transpulmonary gradient is unaffected by the respiratory swings, when its components are measured at the same time point in the respiratory cycle.

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ONLINE SUPPLEMENT

Post-processing of pressure waveforms

The recorded pressure tracings were visually checked and 30 seconds of good quality pressure waveforms were selected near the end of each workload as well as the part with the PCPW tracing. At each workload we selected the PAP tracing as close as possible to the PCPW tracing to minimize changes in flow and ITP between the two measurements. Each selected timeframe was analysed by the use of a home-build program for Matlab (The MathWorks, Natick, MA) in two different methods.

The first methods was a beat-to-beat analysis aimed to separate inspiratory and expiratory heartbeats and to calculate transmural mPAP ($mPAP_{tm}$) and PCWP ($PCWP_{tm}$). Heartbeats which fell entirely in a steady expiratory or inspiratoryphase, determined based on the esophageal pressure, were selectedmanually. In other words, heartbeats which fell during a change in ITP from inspiration to expiration were excluded, as it is difficult to acquire valid pressures from these waveforms. This way systolic (sPAP), mean (mPAP) diastolic (dPAP) of the selected heartbeats as well as the mean right atrial pressure (mRAP) and esophageal pressure (P_{eso}) at the timeframe of the selected heartbeats were automatically acquired. $mPAP_{tm}$ was calculated for each heartbeat as mPAP – P_{eso}. All pressures were averaged for the 10 to 20 inspiratory and 10-20 expiratory heartbeats separately. The swing of all pressures was calculated as the difference between the expiratory and inspiratory values. From the PCWP tracing, inspiratory and expiratory parts were divided based on the espohageal pressure tracing. $PCWP_{tm}$ was calculated as PCWP-P_{eso}.

With the second method we aimed to measure the electronic mean of mPAP ($mPAP_{averaged}$) and PCWP ($PCWP_{averaged}$) by calculating an average value over the entire selection of pressure tracings.

As last, we manually traced the nadir of RAP during expiration (RAP_{nadir}).

Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension

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ABSTRACT

Background

Pulmonary hypertension (PH) is a well-recognized complication of chronic obstructive pulmonary disease (COPD). The impact of PH on exercise tolerance is largely unknown. We evaluated and compared the circulatory and ventilatory profiles during exercise in COPD-patients without PH, with moderate PH and with severe PH.

Methods

Forty-seven patients, GOLD-stages II-IV, underwent cardiopulmonary exercise testing and right heart catheterisation at rest and during exercise. Patients were divided into three groups based on mean pulmonary artery pressure at rest: no PH (mPAP<25 mmHg), moderate PH (mPAP 25–39 mmHg) and severe PH (mPAP≥40 mmHg). Mixed venous oxygen saturation (SvO_2) was used for evaluating the circulatory reserve. Arterial carbon dioxide tension ($PaCO_2$) and the calculated breathing reserve were used for evaluation of the ventilatory reserve.

Results

Patients without PH (n=24) had an end-exercise SvO_2 of 48±9%, an increasing $PaCO_2$ with exercise and a breathing reserve of 22±20%. Patients with moderate PH (n=14) had an exercise SvO_2 of 40±8%, an increasing $PaCO_2$ and a breathing reserve of 26±15%. Patients with severe PH (n=9) had a significantly lower end- exercise SvO_2 (30%±6), a breathing reserve of 37±11% and an absence of $PaCO_2$ accumulation.

Conclusion

Patients with severe PH showed an exhausted circulatory reserve at the end of exercise. A profile of circulatory reserve in combination with ventilatory impairments was found in COPD-patients with moderate PH or no PH. The results suggest that pulmonary vasodilation might only improve exercise tolerance in COPD patients with severe PH.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) have a decreased ability to exercise, which is usually attributed to deconditioning and a decreased ventilatory reserve.[1,2] It has been suggested that a low cardiac output and impaired oxygen delivery to the muscles can contribute to exercise intolerance in COPD[3,4], since stroke volume in the disease is low and stroke volume augmentation during exercise is impaired.[5-9] While pulmonary hypertension (PH) may restrict stroke volume augmentation during exercise, it is still unclear whether in COPD the mere presence of PH contributes to exercise intolerance. In general, COPD associated PH is mild (at least under resting conditions) and develops in patients with a severely impaired pulmonary function.[10] Thus far, studies with vasodilator treatment in patients with mild to moderate COPD-associated PH failed to show an increase in exercise capacity or oxygen delivery, despite an effective decrease in pulmonary vascular resistance.[11,12] This suggests that even in presence of mild to moderate PH, most COPD patients suffer from exercise intolerance due to an exhausting ventilatory reserve. The situation may be entirely different, however, in the subgroup of COPD-patients with severe PH. This subgroup was identified in two large series and characterised by moderate airway obstruction and marked hypoxemia.[13,14] We hypothesized that, unlike patients with mild to moderate PH, the subgroup of COPD-patients with severe PH has a cardiocirculatory exercise limitation, as reflected by an exhausted cardiocirculatory reserve near the end of exercise. The aim of this study was to evaluate and compare the hemodynamic, ventilatory and gas exchange profiles during exercise in COPD patients without PH, with moderate PH and with severe PH. A mixed venous oxygen saturation (SvO_2) at end-exercise near the value measured in healthy subjects was taken as evidence for a circulatory limitation. A ventilatory limitation was assumed in case of an increase in arterial carbon dioxide tension ($PaCO_2$) or an exhausted breathing reserve.

METHODS

Patients

Subjects were either recruited from the local outpatient clinic or referred by other hospitals for the evaluation of PH. Subjects were diagnosed with moderate to very severe COPD according to ATS/ERS criteria.[15] Exclusion criteria were 1) a history of left-sided cardiac failure, 2) left ventricular dysfunction and/or valvular disease on Doppler echocardiography, 3) atrial fibrillation, 4) neuromuscular disorders or 5) an acute exacerbation of COPD within 4 weeks prior to inclusion. The study had institutional review board approval (Medical ethical review committee VU University Medical Center, registration number: NL30766.029.10). All subjects were informed and gave written consent to the procedures. Seventeen patients also participated in a studies on the acute of sildenafil in COPD [12,16]. Twenty-one other patients participated in a study on the effect of airflow limitation and pleural pressure on the pulmonary circulation in COPD[17].

Based on the resting mean pulmonary artery pressure (mPAP) patients were divided into three groups: (1) no PH (mPAP<25 mmHg), (2) moderate PH (mPAP 25–39 mmHg) and (3) severe PH (mPAP≥40 mmHg). The cut-off values were based on the current definition of PH (≥25 mmHg)[18] and the suggested definition of out-of-proportion PH (≥ 40 mmHg)[13]. All patients underwent CT and V/Q scanning in order to rule out thrombo-embolic disease. All patients had a wedge-pressure below 15 mmHg, which excludes left-ventricular

dysfunction. Because it has been shown that patients with idiopathic pulmonary arterial hypertension frequently exhibit some degree of airflow limitation[19], we only included patients with emphysema on the HRCT in order to ensure the presence of COPD.

Pulmonary function measurements

Spirometry, body-plethysmography and single-breath carbon monoxide diffusing capacity (DLCO) (Vmax, Sensormedics, Yorba Linda, CA) were measured according ERS guidelines.[20-22] All pulmonary function measurements were obtained, within two days of the hemodynamic measurements.

Cardio-pulmonary exercise test (CPET)

Patients performed a standardized, incremental maximal exercise test using an electromagnetically braked cycle-ergometer (Ergoline GmbH, Bitz, Germany) according to the ATS/ACCP guidelines.[23] Breath-by-breath measurements were made of oxygen consumption (VO_2), carbon dioxide output (VCO_2) and ventilation (VE) (Vmax229, Sensormedica, Yorba Linda, CA, USA). Ventilatory equivalents for CO_2 was calculated. Heart rate and gas exchange were recorded during 3 minutes of rest, 3 minutes of unloaded pedalling at 60 rpm followed by a progressive increase in workload of 5-20 watt every minute until exhaustion. The chosen protocol was based on the patient's medical history (daily life exercise performance) in combination with pulmonary function results, thereby aiming at a duration of the test between 6 and 15 minutes. The anaerobic threshold was determined using the v-slope method.[24] Maximal voluntary ventilation (MVV) was calculated as $40*FEV_1$ and the breathing reserve was noted in absolute numbers (liters/min) or as (MVV-VEmax)/MVV*100% [25]. Six-minute-walking distance was measured according to the established guidelines.[26]

Exercise hemodynamics

A balloon-tipped, flow directed 7.5 Fr, Swan-Ganz catheter was inserted via the jugular vein into the pulmonary artery under local anaesthesia. All patients were in stable condition under continuous monitoring of heart rate and oxygen saturation. After placement of the pulmonary artery catheter, a second catheter was inserted into the radial artery. With the pulmonary artery catheter and arterial line in position, patients were placed either on the same electromagnetically braked cycle-ergometer as used during CPET in supine position or positioned on a recumbent bicycle (Lode, Groningen, The Netherlands) while lying on a bed. After at least five minutes of supine rest, measurements were made of the following variables: pulmonary artery, right atrial, arterial and pulmonary capillary wedge pressures and heart rate together with sampling of arterial and mixed venous blood. Subsequently, patients exercised at a fixed workload, which was chosen to 1) attain a heart rate of at least 80% of the peak heart rate as determined during CPET and to 2) allow sufficient time for hemodynamic measurements (approximately five minutes of exercise). The chosen workload was applied at once or via less than two intermediate workloads depending on the patients' physical condition. During the last minute of exercise measurements were made of pulmonary artery pressure, heart rate and oxygen consumption together with sampling of exercise: mixed venous and arterial blood. Patients were instructed to signal just before exhaustion in case they were unable to fulfil exercise for 5 minutes, in order to finish data collection. Afterwards cardiac output (CO, direct-Fick-method), stro-

ke volume (CO/Heart Rate), and pulmonary vascular resistance ((PVR=mPAP-PCWP)/CO) were calculated. Slope of CO and VO_2 (CO/VO_2-slope) was calculated as the change in CO from rest to exercise divided by the change in VO_2.

Statistical methods

Hemodynamic, pulmonary function and exercise parameters are presented as mean ± standard deviation unless stated otherwise. Comparisons of rest and peak measurements between the three groups were performed by a one-way-ANOVA with Bonferroni post-hoc correction. In case of a non-normal distribution a Kruskal-Wallis test was used. Comparisons of rest-to-exercise responses were performed with a two-way-ANOVA with Bonferroni post-hoc correction. Analyses were performed with GraphPad Prism for Windows version 5.0 or SPSS for Windows version 15.0. A p-value <0.05 was considered significant.

RESULTS

		No PH	Moderate PH	Severe PH
N		24	14	9
Age	**(yr)**	62 ± 14	68 ± 9	66 ± 8
Sex	**men/women**	14/10	4/10	7/2
FEV_1	**(L)**	1.4 ± 0.52	1.02 ± 0.40	1.65 ± 0.55 †
Length	**(cm)**	175 ± 7	168 ± 7	173 ± 8
Weight	**(kg)**	76 ± 12	74 ± 16	80 ± 23
FEV_1	**(% pred)**	49 ± 18	43 ± 13	55 ± 17
FEV_1/VC	**(%)**	40 ± 16	37 ± 9	44 ± 11
VC,	**(l)**	3.49 ± 0.8	3.04 ± 1.16	3.89 ± 1.10
FRC	**%**	162 ± 40	151 ± 22	133 ± 33
TLC	**(% pred)**	125 ± 19	119 ± 19	106 ± 19 °
DLCO/VA	**(% pred)**	65 ± 20	61 ± 20	41 ± 17 °
PaO_2	**(mm Hg)**	71 ± 11	57 ± 12 °	56 ± 10 °
$PaCO_2$	**(mm Hg)**	38 ± 5	44 ± 10	37 ± 10
mPAP	**(mm Hg)**	19 ± 3	31 ± 4	51 ± 9
PCWP	**(mm Hg)**	7 ± 2	10 ± 3 °	11 ± 5 °
CI	**(l/min/m^2)**	3.2 ± 0.7	3.3 ± 0.8	2.5 ± 0.4 ° †

Table 5.1 ***Demographic, pulmonary function and hemodynamic characteristics of study***
FEV_1: Forced Expiratory Flow in 1st second, VC: Vital Capacity, TLC: Total Lung Capacity, RV: Residual Volume, FRC:, DLCO: Diffusion Capacity of the Lungs for Carbon Monoxide, PaO_2: Arterial oxygen tension, $PaCO_2$: Arterial carbon dioxide tension mPAP: mean Pulmonary artery pressure, PCWP: Pulmonary capillary wedge pressure, CI: Cardiac Index, PVR: Pulmonary vascular resistance
† $p < 0.05$ vs. No PH, † $p<0.05$ vs. No PH
° $p < 0.05$ vs. No PH, † $p<0.05$ vs. Moderate PH

Study population

Forty-seven COPD-patients (25 men, 22 women; mean age 65 yrs) were included. Twenty-four patients had no PH, fourteen patients had moderate PH and nine patients had severe PH. Demographic data, pulmonary function and resting hemodynamics are summarized in table 5.1.

Incremental Cardiopulmonary Exercise Test

Characteristics of the three groups are presented in table 5.2 and figure 5.1. The subjects had a severe impaired exercise capacity, as evidenced by peak work rates and VO2's that were, on average, <50% predicted and <15 ml/kg/min, respectively. Maximal power and oxygen uptake were higher in patients without PH than in patients with moderate or severe PH. All three groups showed an identical heart rate reserve. The respiratory quotient (RQ) at maximal exercise was lower in patients with moderate PH (0.91±0.08) than in patients without PH (1.01±0.11) and patients with severe PH (1.05±0.16). An anaerobic threshold could be identified in 10 out 23 patients without PH, 2 out of 14 patients with moderate PH and in 5 out of 9 patients with severe PH. End-tidal CO_2 was significantly lower in the severe PH group than in patients without PH or with moderate PH. Similarly,

ventilatory equivalents for CO_2 and O_2 were higher in patients with severe PH. The ventilatory reserve tended to be larger in patients with severe PH than in the other two groups (p=0.09). Inspiratory capacity reduced from rest to exercise in all three groups with respectively 0.73 ± 0.44L, 0.49 ± 0.37 L and 0.60 ± 0.42 L. Exertional symptoms in the group without PH included intolerable dyspnoea in 23 patients and predominantly leg fatigue in one patient. Patients with moderate PH reported intolerable dyspnoea (8 patients), leg fatigue (2 patients) and dizziness (3 patients) as reasons to terminate exercise. Patients with severe PH reported intolerable dyspnoea (6 patients) and leg fatigue (3 patients).
The 6 minute-walking-distance was not different between patients without PH (407±88m) and with moderate PH (338±82m), but significantly lower in patients with severe PH (208±144m, p<0.01).

	No PH (n=24)	Moderate PH (n=14)	Severe PH (n=9)	Limits of Normal
Maximal Work (W)	71±47	47 ± 33	28 ± 17°	91 - 229
VO_{2_max} (ml/kg/min)	14.0±4.2	10.2±3.0	9.2 ± 2.8	18 - 35
$HR_{\_max}$ (bpm)	125±17	113±28	111±13	143 -172
Respiratory Quotient	1.01±0.11	0.91 ± 0.08 °	1.05 ± 0.16 †	1.15 – 1.25
VE_{max} (L/min)	41±13	26±10	42±14	77 - 158
MVV-VE (L)	*14 ± 14*	*10 ± 9*	*26 ± 16* †	> 11
VE/MVV (%)	78 ± 21	77 ± 18	63 ± 12	
SaO_{2_Rest} (%)	95 ± 3	89 ± 4 °	87 ± 5 °	95 - 100
SaO_{2_Max} (%)	90 ± 6	81 ± 5 °	81 ± 8 °	95 - 100
f_{R_peak} (breaths/min)	30±7	32 ± 5	30±4	< 55
Vt_{rest} (L)	0.7 ± 0.2	0.5 ± 0.4	1.0 ± 0.5 ° †	
Vt_{max} (L)	1.4 ± 0.5	0.78 ± 0.6 °	1.5 ± 0.5 †	
$pET\_CO_{2\_rest}$ (mm Hg)	30 ± 5	35 ± 7	24 ± 11 †	36 - 42
$pET\_CO_{2\_max}$ (mm Hg)	36 ± 8	39 ± 9	22 ± 13 ° †	36 - 42
VE/VCO_2-slope	34 ± 11	37 ± 21	72±44 ° †	33 - 37
	No PH (n=12)	**Moderate PH (n=9)**	**Severe PH (n=6)**	
IC_{rest} (L)	2.71 ± 0.75	1.86 ± 0.67 °	2.20 ± 0.66	
IC_{max} (L)	1.94 ± 0.52	1.36 ± 0.37	1.60 ± 0.43	
IRV_{max} (L)	0.44 ± 0.22	0.54 ± 0.24	0.47 ± 0.20	

Table 5.2 ***Parameters from the CPET***
Shown are the absolute values with percent of predicted value in parentheses. Range of values between square brackets. VO2: Oxygen consumption, HR: Heart Rate, VE: Minute ventilation, MVV: maximal voluntary ventilation, fR: breathing frequency, pET_CO2: End-Tidal carbon dioxide pressure, VE/CO_2–slope: mean regression slope relating minute ventilation to carbon dioxide production. IC: inspiratory capacity, Vt: tidal volume, IRV: inspiratory reserve volume. Please note that measurements of IC were only performed in the last 27 consecutive patients. ° p < 0.05 vs. No PH, † p<0.05 vs. Moderate PH. Limits of normal from ref 23

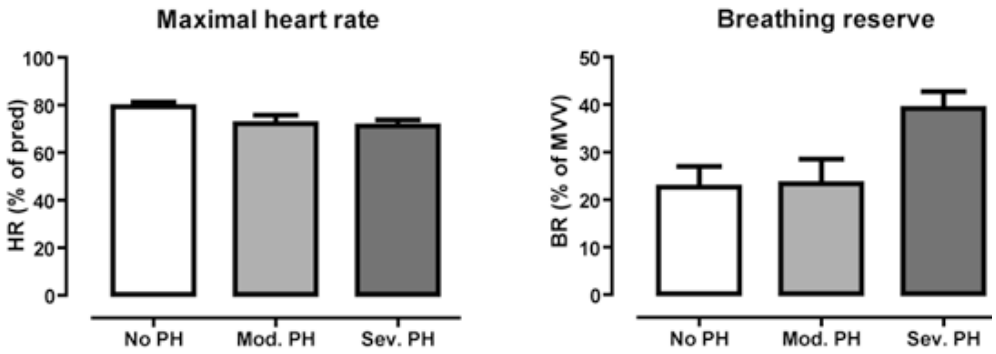

Figure 5.1 ***Classical exercise limitation parameters from the CPET in the three groups of COPD-patients.***
HR = Heart Rate, BR = Breathing reserve. Note that none of the 3 groups reaches the predicted maximal heart rate. The breathing reserve at end-exercise seems normal in the patients with severe PH, were it is lowered in the patients without or with moderate PH. Between the groups there is, however, no significant difference (p=0.09)

Invasive exercise protocol

During exercise with hemodynamic measurements patients reached 94±11% of the previously measured maximal heart rate achieved during CPET. Results of the hemodynamic measurements are shown in table 5.3 and figure 5.2. Peak heart rate in the three groups reached respectively 76 ± 13%, 77 ± 11% and 73 ± 8% of the predicted maximum. SvO_2 at the end of exercise reached 30±5% in the patients with severe PH and remained higher in patients with moderate PH (41±8%) or without PH (48±9%) or. This indicates a reserve in oxygen extraction in the latter two groups. SVI was not different between patients without PH and with moderate PH, but was lower in patients with severe PH both at rest and at end-exercise. The CO/VO_2-slope was lower in patients with severe PH compared to patients without PH ($p<0.05$), whereas the slope in patients with moderate PH was not statistically significant from the other groups.

$PaCO_2$ increased significantly during exercise in patients without ($p<0.001$) or with moderate PH ($p<0.001$), whereas $PaCO_2$ was significantly lower in patients with severe PH at rest, compared to moderate PH, and did not change with exercise. ($p_{interaction}<0.001$). Patients with moderate and severe PH had a lower SaO_2 at rest (both $p<0.01$) and showed a more pronounced desaturation during exercise than patients without PH ($p_{interaction}<0.001$). It could be argued that patients with an mPAP between 35 and 40 mmHg should be classified in the group with severe PH. Three of our study patients fell in this category and all had severe airway obstruction with FEV_1-values of 0.68, 0.73 and 1.18 L. (31, 33 and 41 % of predicted). All had an exercise response comparable with patients with a mPAP<35 mmHg, with a predominantly ventilatory impairment characterised by $PaCO_2$-accumulation, an SvO_2 at end-exercise of respectively 37, 37 and 35 % and low breathing reserves of 22, 24 and -10%.

	No PH		Moderate PH		Severe PH		
	Rest	Exercise	Rest	Exercise	Rest	Exercise	$p_{interaction}$
CI (l/m^2)	3.2 ± 0.7	5.5 ± 1.7	3.3 ± 0.8	4.9 ± 4.5	2.5 ± 0.4	3.3 ± 1.0°°°††	**<0.01**
SVI (ml/m^2)	40 ± 12	49 ± 11	40 ± 11	43 ± 11	31 ± 11 °°†	32 ± 9°°°†	0.07
mPAP(mmH g)	19 ± 3	35 ± 11	31 ± 4°°°	52 ± 13°°°	51 ± 9°°°†††	69 ± 11°°°†††	0.42
SaO_2 (%)	94 ± 3	91 ± 5	88 ± 5°°	79 ± 8°°°	90 ± 5°°	80 ± 9°°°	**<0.001**
SvO_2 (%)	69 ± 4	48 ± 10	65 ± 7	41 ± 8°°	55 ± 10°°°†††	30 ± 5°°°††	0.50
$PaCO_2$ (mmHg)	38 ± 5	41 ± 6	45 ± 10	49 ± 10	37 ± 10	35 ± 10††	**<0.01**

Table 5.3 ***Exercise hemodynamic and gas exchange parameters***
CI: Cardiac Index, SVI: Stroke Volume Index, mPAP: mean Pulmonary Artery Pressure, SaO2: Arterial oxygen saturation, SvO2 : Mixed venous oxygen saturation. PaCO2 : arterial carbon dioxide tension. ° p < 0.05 vs. No PH, °°° p<0.001 vs. No PH, † p<0.05 vs. Moderate PH, †† p<0.01 vs. Moderate PH, ††† p<0.001 vs. Moderate PH

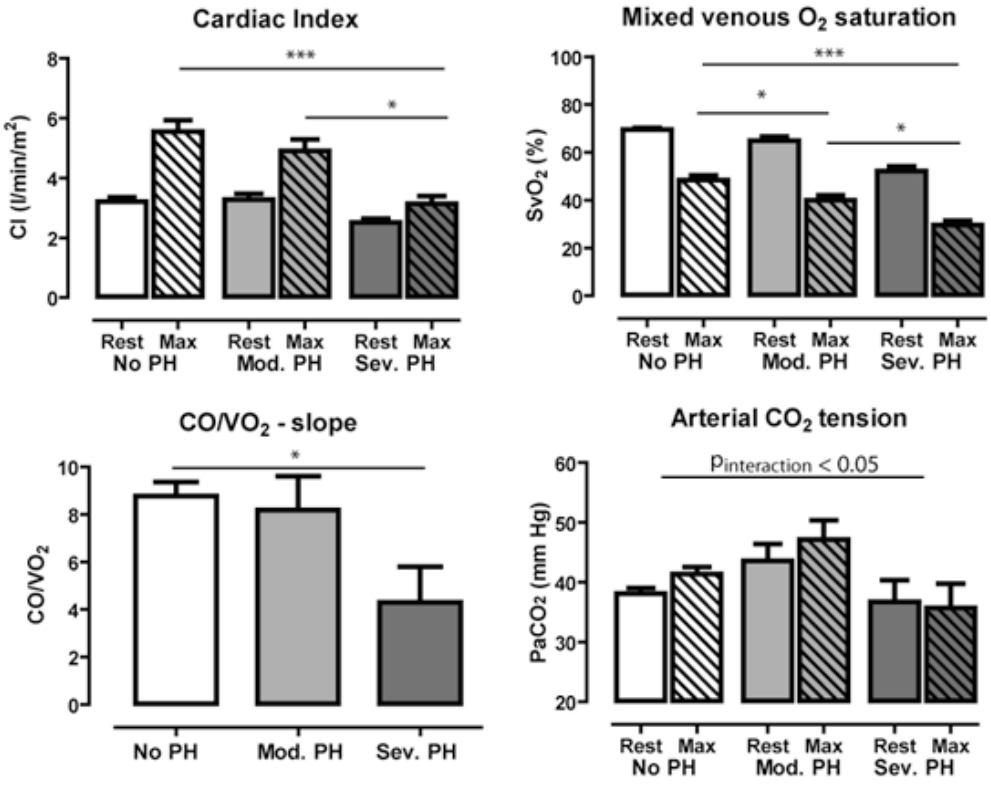

Figure 5.2 ***Hemodynamic parameters and gas exchange parameters acquired at rest and the last minute of exercise.***
CI = cardiac index, SvO_2 = mixed venous oxygen saturation, SaO_2 = arterial oxygen saturation, CO/VO_2 – slope : Slope of cardiac output and oxygen consumption from rest to exercise. $PaCO_2$ = Arterial carbon dioxide tension, Note the low end-exercise mixed venous oxygen saturation and the lowered CO/VO_2-slope in patients with severe PH, indicating an exhausted circulatory reserve. This is in contrast with the two other groups.

DISCUSSION

In this study we used CPET data combined with invasive hemodynamic measurements at rest and during maximal exercise to evaluate whether PH contributes to exercise intolerance in COPD. Only in COPD patients with severe PH, the SvO_2 at end–exercise decreased to a level usually found in healthy subjects[27,28], which is consistent with reaching a circulatory limitation. Together with the finding of a low CO/VO_2-slope, we can conclude that these patients had exhausted their circulatory reserve. In addition, without accumulation of $PaCO_2$ and an average breathing reserve of 37%, this group of patients had no demonstrable ventilatory limitation. Like the other groups of COPD patients, the patients with severe PH showed significant dynamic hyperinflation: the IRV in these patients reached a level which is known to induce dyspnoea[29]. However, the decline in $PaCO_2$ at the end of exercise in these patients suggests that an exhausted circulatory reserve was the major exercise limiting factor limiting exercise. In contrast, COPD-patients with no or with moderate PH predominantly showed signs of a ventilatory limitation to exercise, with an increase in $PaCO_2$ and a reduced ventilatory reserve. The higher SvO_2 at maximal exercise and a normal CO/VO_2-slope suggest that these patients still had a circulatory reserve.
A low SvO_2 at maximal exercise is a strong indicator of a circulatory exercise limitation and depends on SaO2 as well as maximal cardiac output and peripheral oxygen extraction.[30] SaO_2 decreased to a similar extent in patients with moderate and severe PH and could therefore not account for the lower SvO_2 at the end of exercise in patients with severe PH. In COPD, deconditioning could potentially hamper peripheral oxygen extraction, which would translate into a relatively high SvO_2 near the end of exercise. There is no reason to assume, however, that deconditioning in COPD patients with severe PH would be less severe than in COPD patients with moderate PH. Moreover, Richardson et al. [31] showed by single leg exercise tests, that when freed from central constraints, peripheral oxygen extraction of the peripheral muscles can increase in COPD. We therefore assume that the difference in maximal oxygen extraction between patients with moderate PH and severe PH is caused rather by a difference in circulation than by a difference in ability of the peripheral muscles to extract oxygen. Peak heart rate in these patients did not reach the predicted maximal value. However, since it is well known that patients with pulmonary arterial hypertension do also have a significant heart rate reserve at maximal exercise (30-32), this observation does not argue against a circulatory impairment in the group with severe PH. Therefore, the SvO_2 and CO/VO_2-slope during exercise provide better insight in the presence of a circulatory limitation to exercise in patients with PH.

Severe PH in COPD is rare. It is found in approximately 1-4% of patients with COPD[13,14]. The high percentage of severe PH in our study is due to the tertiary referral function for pulmonary hypertension of our hospital. Therefore, no conclusions should be drawn from this study concerning the prevalence and average severity of PH in COPD. All our patients with severe PH had moderate to very severe airway obstruction, emphysema on the HRCT and an average smoking history of 35 years. We defined the lower level of severe PH as mPAP ≥ 40 mmHg based on the study of Chaouat et al.[13] As there is no consensus about the lower limit of severe or out-of-proportion PH, we individually evaluated patients with a mPAP between 35 and 40 mmHg. All these patients showed exercise profiles similar to the other patients with moderate PH.
In accordance with previous studies[13,14], patients with COPD associated severe PH were

characterised by a low DLCO, a normal to low $PaCO_2$ and hypoxemia, and a relatively preserved pulmonary function (see table 5.1). Here we show for the first time that $PaCO_2$ remains low during exercise in these patients, which contrasts to the elevation in PaCO2 commonly found during exercise in COPD. Non-invasive CPET markers of severe PH in our study were increased ventilatory equivalents for carbon dioxide and a low end-tidal carbon dioxide tension, as shown in figure 5.3. The increase in minute ventilation in COPD patients with severe PH mainly resulted from an increase in tidal volume. Relative hypocapnia due to alveolar hyperventilation has been described in patients with pulmonary arterial hypertension[32], but the reasons are poorly understood. Suggested causes include increased sympathetic nerve system activity[33] and a hypoxic ventilatory drive [32]. It is possible that during exercise in our COPD patients with severe PH, alveolar ventilation was augmented due to increased acid production in the context of an exhausted cardiocirculatory reserve. It can be argued that circulatory impairments may contribute to exercise intolerance in COPD by augmenting the ventilatory drive, thereby decreasing the time to reach a critical mechanical constraint on exercise ventilation and accelerating the onset of intolerable dyspnea. This increased ventilatory drive together with pulmonary function impairments and the presence of dynamic hyperinflation may explain why COPD-patients with severe PH experience severe (exertional) dyspnea.[13]

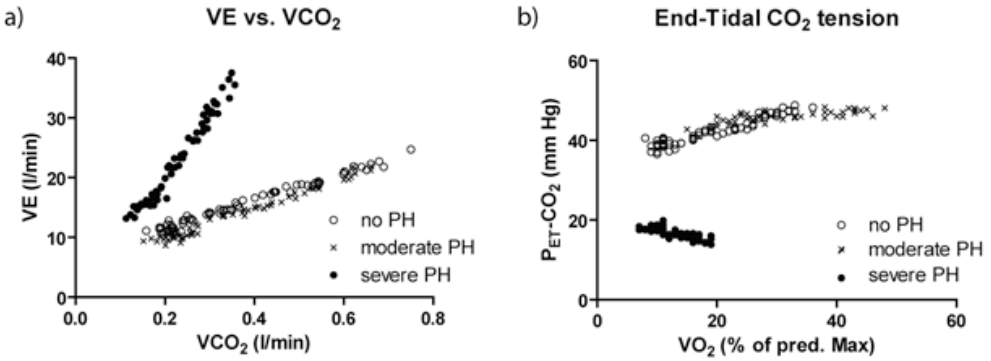

Figure 5.3 ***CPET-measurements of three different COPD-patients.*** *Shown are patients without PH (open circles, male, age 67, FEV_1: 28% of predicted, mPAP: 14 mm Hg) with moderate PH (x, female, 62 year old, FEV_1: 31% of predicted, mPAP: 32 mm Hg) and with severe PH (solid circles, male, age 55, FEV_1: 31% of predicted, mPAP: 52 mm Hg). The exercise protocol consisted of 3 minutes of rest, 3 minutes of unloaded cycling and incremental workload increase of respectively 10, 10 and 5 Watt / minute until exhaustion. a) Minute ventilation vs. carbon dioxide production. b) End-Tidal CO_2 vs. O_2 consumption as a percentage of the predicted maximum.*

The presence of moderate PH in COPD-patients did not appear to result in a lowered CO/VO_2-slope during exercise and was associated with a higher SvO_2 at the end of exercise. The presence of a circulatory reserve at end-exercise in these patients leads us to conclude that moderate PH does not directly affect exercise capacity. This finding is in line with previous, non-invasive studies[34,35]. A normal CO/VO_2-slope in COPD patients without and with moderate PH is also in accordance with previous studies. Light et al.[6] showed that although heart rate increased more rapidly from rest to exercise in COPD-patients (average mPAP:

23 mm Hg), the CO/VO_2-slope was not different from normal elderly people. Biernacki et al. [36] concluded on the basis of invasive measurements in 100 COPD-patients that, despite the presence of moderate pulmonary hypertension, the majority of patients have a normal cardiac output at rest and a normal CO-response during exercise. A CO/VO_2-slope within the normal limits in COPD was also found by others.[4,37] In contrast with these previous studies we divided the patients based on the pulmonary artery pressure at rest and were able to evaluate the response to exercise in patients with severe PH separately from patients with moderate PH or without PH. By combining ventilatory and circulatory data during exercise enabled us to identify a PH-induced circulatory impairment in patients with severe PH. The presence of a circulatory limitation in patients with severe PH indicates that lowering pulmonary vascular resistance may improve exercise tolerance in these patients. There has been increasing interest in the possible role of PH-specific medication in more common forms of PH, especially PH related to COPD. The exercise profiles of patients with no or only moderate PH in the present study indicate that the exercise tolerance of these patients will likely not benefit from pulmonary vasodilating therapy. The first studies evaluating PH-medication in COPD-patients without and with moderate PH showed no improvement in exercise capacity or O_2-delivery despite successful lowering of the PH..[11,12,16,38] Future studies evaluating PH-specific medication should aim at the group of out-of-proportion PH only.

STUDY LIMITATIONS

The most important limitation of this study is that reliable hemodynamic measurements cannot be made during a maximal, incrementally increasing exercise test. Therefore patients performed a constant workload test. However, by choosing the right workload based on the CPET and applying 1 or 2 intermediate steps we were able to perform hemodynamic measurements at a high (close to maximum) exercise intensity.

Determination of dynamic hyperinflation was not performed in all patients. At the time of inclusion of the first 20 patients, IC-measurements were not yet routinely performed in our exercise laboratory. Here we show measurements completed in the last 27 patients and since these patients were distributed equally over the three groups, a selection bias is unlikely. Even though all patients underwent careful diagnostics to exclude pulmonary embolism and left failure, the most common causes of out of proportion pulmonary hypertension as shown by Chaout et al [13], it cannot be completely ruled out that some of the included patients had pulmonary hypertension unrelated to COPD. In the group with severe PH, one patient was diagnosed with mild OSAS and one patient with a limited degree of fibrotic changes on HRCT, in addition to emphysema. Exercise characteristics at the AT were not provided in this study since gas exchange measurement did not allow determination of the AT in about half of the patients (which is in accordance with previous studies[39 40]).

Twenty-three patients exercised in the supine position and twenty-four in a semi-recumbent position. This slight difference in body position was distributed evenly over the three groups. Gender, pulmonary function and arterial oxygen tension differed between the groups. Because the used criteria for either a ventilatory or a circulatory limitation to exercise are not different for males and females, we do not think that the uneven sex distribution in our study was responsible for the observed differences between the three study groups. Patients with moderate PH had the most severe pulmonary function impairment.

The hypoxemia in this group was most likely due to V/Q-mismatching. Patients with COPD and severe PH are known to have better pulmonary function, but severe hypoxemia.[13,14] The exact mechanisms of hypoxemia in this group of patients remains to be elucidated.

CONCLUSION

The present study shows a PH-induced circulatory limitation to exercise in COPD-patients with a mPAP≥40 mmHg. In COPD-patients without or with moderate PH, the exercise profile indicates a circulatory reserve and a predominantly ventilatory limitation to exercise.

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Author's contributions

BGB, HR, BH, HG, AB, PEP and AVN, contributed to conception and design of the present study. BGB, PT, HG, HR and BH, contributed to the acquisition of data. BGB, PT, HG, HJB, NW, AVN contributed to analysis or interpretation of the data. BGB, HJB, AVN drafted the manuscript, and PT, HG, HR, BH, AB, NW, PEP revised the article critically for intellectual content. All authors gave their final approval of this version of the manuscript to be published.

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Letter:

Cardiac shunt in COPD as a cause of severe hypoxemia: probably not so uncommon after all.

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TO THE EDITORS

Hypoxemia is a common finding in Chronic Obstructive Pulmonary Disease (COPD) and may aggravated during exercise. The main mechanism is perfusion through not well ventilated areas; a ventilation-perfusion mismatch. True shunting defined as venous blood directly mixing with end-capillary blood at the arterial side of the circulation is not a usual cause of hypoxemia in COPD [1, 2]. The amount of shunting related to ventilation-perfusion mismatch is usually made by the calculation of the shunt fraction while the patient is inhaling 100% oxygen. We present two cases of severe hypoxemia in patients with COPD to show that a cardiac shunt can contribute to hypoxemia and that this shunt can be missed if the 100% oxygen method is used to quantify shunt.

Patient A is a 68-year old man, referred from another hospital to our clinic for evaluation of severe dyspnoea and hypoxemia. Patient complaints were fast-progressive dyspnoea and severe impaired exercise tolerance with blue discoloration of fingers and lips since 3 months. There were no complaints of coughing, sputum production or fever. Patient quitted smoking 12 years ago after 60 pack years. Physical examination revealed a man with peripheral and central cyanosis and a little ankle edema. Arterial blood gases revealed a hypoxemia at rest with a PaO_2 of 42 mmHg and a SaO_2 of 77%. Pulmonary function test showed moderate obstruction (FEV_1: 67% FEV_1/SVC:65% of predicted). Initiation of exercise resulted in immediate oxygen desaturation till 71%, preventing any further exercise. Radiologic analysis by means of High Resolution CT, Pulmonary Angiography and Ventilation-Perfusion scan revealed only signs of emphysema. Transthoracic and transoesophageal echocardiography, showed dilatation of the right atrium and ventricle with signs of pulmonary hypertension. No signs of an intracardiac right-to-left shunt were seen. Both tests were performed while 15 liter oxygen per minute was administered. Right heart catheterisation confirmed the diagnosis of pulmonary hypertension (see table 6.1). The response to administration of 100% oxygen was a fall of mPAP to 24 mmHg, accompanied by a significant increase in arterial oxygenation to 98%.

	Patient B			Patient B		
	Normal	100% O_2	NO	Normal	100% O_2	NO
PAP s/d/m (mmHg)	52 / 25 /37	39 /13 /24	44/13/26	56 /23 /37	41 /19 /26	41/13/25
PCWP (mmHg)	4	-	-	15	-	-
PVR (dynes/sec/cm)	559	246	185	234	142	118
RAP (mmHg)	10	-	-	10	-	-
RVDP (mmHg)	13	-	-	13	-	-
Cardiac Output (L/min)	4.7	6.5	8.5	7.5	6.2	6.8
Hart frequency (beats/min)	100	105	99	66	59	65
Stroke Volume (ml)	47	62	85	114	105	105
SaO_2 (%)	89	96	93	81	99	96
PaO_2(mmHg)	52	105	159	48	229	72
SvO_2 (%)	58	69	80	51	77	75

Table 6.1 ***Hemodynamic characteristics while breathing room air , 100% Oxygen and Nitric Oxide.***
NO= Nitric Oxide: 20 ppm, PCWP: Pulmonay capillary wedge pressure, RVDP: Right ventricular diastolic pressure, RAP: mean right atrial pressure, SaO2: Arterial Oxygen saturation, PaO2 Arterial Oxygen pressure, SvO2 Mixed venous oxygen saturation

For this reason we assumed that a right-to-left shunt through a Patent Foramen Ovale (PFO) was present under normoxic conditions and during exercise, although no intracardiac shunt was seen during echocardiography. A cardiac MRI was performed while the patient was breathing room air. Flow per beat was measured over the pulmonary artery (44 ml) and aorta (56 ml), which resembles a right-to-left shunt of 25%. We concluded from these measurements that oxygen desaturation during exercise under normoxic conditions occurs as a consequence of right-to-left shunting through a PFO. The patient was referred to the cardiologist for a percutaneous closure of the PFO, which resulted in an improved clinical condition together with an oxygen saturation of 95% at rest which remained unaltered during exercise. Control MRI showed similar flow per beat through the aorta and pulmonary artery (57 ml).

Patient B is a 70-year old man with a history of COPD, hypercapnia and echocardiographic signs of PH. Patient complained of progressive dyspnoea on exercise with blue discoloration of lips and fingers since several months. He experienced no acute exacerbations of his COPD in the last year. Patient quitted smoking 18 years ago. Arterial blood gas analysis showed hypoxemia (PaO_2 38 mmHg, SaO_2: 81%) and hypercapnia (PCO_2: 56 mmHg). Hypercapnia was interpreted as a sign of respiratory insufficiency for which a trial of Bi-level Positive Airway Pressure (BIPAP) treatment was tried in the past, resulting in a further worsening of his hypercapnia and hypoxemia. Pulmonary function test showed severe obstruction (FEV_1: 41% and FEV_1/SVC: 37 % of predicted). During cardiopulmonary exercise testing patient reached 70 Watt (44% of predicted) which led to an oxygen desaturation till 71 % while heart rate reserve was 21% and ventilatory reserve was 50%. For this reason hypoxemia was considered the exercise limiting factor. High Resolution CT, Pulmonary Angiography and Ventilation-Perfusion scan showed severe emphysema without evidence for pulmonary embolisms. Echocardiography, with oxygen (15 l/min), showed dilatation of right atrium and right ventricle and signs of PH. No intracardiac shunt was found. Right

heart catheterisation was performed, which revealed increased pulmonary artery and right atrial pressures (table 6.1). Inhalation of 20 ppm nitric oxide led to a normalisation of pulmonary artery pressure and oxygen saturation. Based on this finding, it was concluded that the severe desaturation during exercise was most likely due to right-to-left shunting through an PFO in the presence of PH secondary to COPD. Echocardiography was repeated under normoxic conditions, showing a PFO at a location unsuitable for percutaneous closure. Because of the good response to inhaled NO a trial of a PDE-5 inhibitor was initiated, leading to clinical improvement and a stable oxygen saturation of 90 %. After 4 years, patient was re-evaluated showing a stable condition with a SaO_2 of 91% at rest with a similar flow per beat through the aorta and pulmonary artery (70 ml) measured with MRI.

DISCUSSION

A PFO is present in 25 to 30 percent of the population, however, will remain without hemodynamic consequences under normal conditions [3]. In case of increased right atrial pressures right-to-left shunting through a PFO might occur, leading to hypoxemia. [4, 5] We presented two cases of right-to-left shunting through a PFO in the presence of PH secondary to COPD in which shunting significantly contributed to the hypoxemia. The PH presumably started shunting through the PFO leading to hypoxemia. With hypoxemia, the oxygen pressure in mixed venous blood also decreased, thereby stimulating hypoxic pulmonary vasoconstriction [6], on its turn leading to an increase in pulmonary artery pressure. This led to a further increase in right atrial pressure and thereby to a larger pressure gradient over the PFO, leading to the vicious circle, as shown in figure 6.1. This mechanism also explains the severe desaturation observed at exercise, since cardiac output augmentation induced by exercise will lead to an increase in pulmonary artery pressure and by that an increase in the right-to-left shunt. Finally, BIPAP might induce an increase of the right to left shunt, as was observed in our second patient, due to its effect on pulmonary artery pressure [7].

In both patients active vasoconstriction contributed to a great extent to pulmonary hypertension as was proven by the effects of the vasodilating agent nitric oxide. Arterial oxygenation improved with vasodilation, being different from large groups of COPD-patients [8, 9]. This provides evidence that the right-to-left shunt was the main mechanism of hypoxemia in our patients. Therefore, it was decided to close the PFO in patient A as a treatment of the cause of the pulmonary hypertension as outlined in figure 6.1.

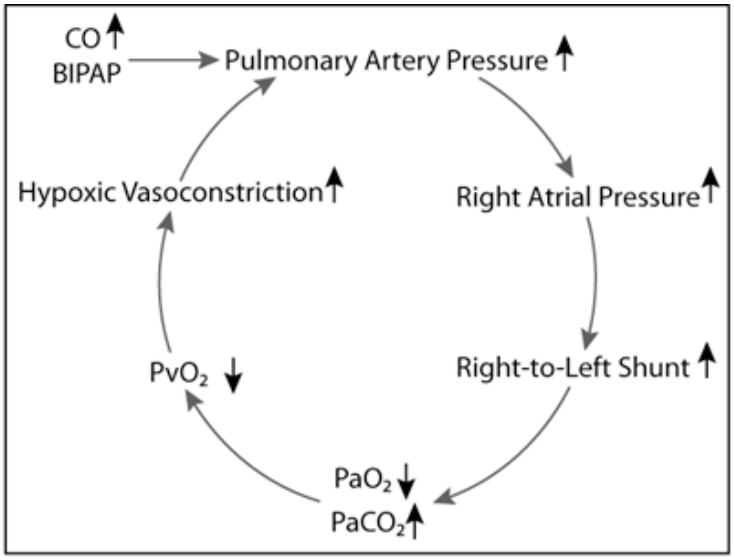

Figure 6.1 *Vicious circle of right-to-left shunting in the presence of pulmonary hypertension secondary to COPD.*
PaO2 : arterial oxygen pressure,
PaCO 2 : arterial carbon dioxide pressure,
PvO2 : mixed venous oxygen pressure,
CO: Cardiac Output BIPAP: Bi-level positive airway pressure

Because of the inability to close the PFO percutaneously in patient B, a trial with a PDE-5 inhibitor was initiated. Although studies revealed no benefit of PDE 5-inhibitors or even worsening of the ventilation-perfusion match in COPD patients [9, 10], we started it based on the beneficial response to inhaled NO. Our aim was to lower pulmonary artery and right atrial pressure leading to closure of the PFO. Because of a good response and clinical improvement we decided to continue treatment with the PDE-5 inhibitor. However, from our observations no conclusions should be drawn how we should treat COPD patients with pulmonary hypertension in general. Both patients were already on oxygen treatment which was continued afterwards, since oxygen therapy is the only proven beneficial therapy for COPD and pulmonary hypertension.

Why was initially the open foramen ovale not seen with echocardiography in both patients? Most probably because these measurements were performed at rest with administration of 15 liter oxygen per minute. With the vasodilative effect of oxygen, right atrial pressure, the driving force of the right-to-left shunt, was lowered and the PFO was physiologically closed.

Thus, where pulmonary shunting in patients with COPD is usually not a cause of hypoxemia, right-to-left shunting through a PFO can contribute to the hypoxemia in presence of secondary PH. The importance of the shunting might be underestimated if echocardiographic evaluation is performed while the patient uses high fraction oxygen therapy. Traditionally, it is assumed that a trial with a high inspiratory fraction of oxygen is a good measure to quantify shunt. Our two cases showed that in case of COPD this rule does not always apply.

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Progressive Dilatation of the Main Pulmonary Artery is a Characteristic of Pulmonary Arterial Hypertension and is Not Related to Changes in Pressure

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ABSTRACT

Background

Pulmonary Artery Dilatation is one of the consequences of Pulmonary Arterial Hypertension (PAH) and is used for non-invasive detection. However, it is unclear how the size of the pulmonary artery behaves over time and if it's related to pressure changes. The aim of this study is to evaluate the pulmonary artery size during follow-up in treated PAH-patients and whether it reflects pulmonary vascular hemodynamics.

Methods

Fifty-one patients with PAH, who underwent at least two Right Heart Catheterizations (RHC) both together with cardiac Magnetic Resonance Imaging, were included in this study. Another eighteen subjects who had normal pressure at RHC were included for comparison at baseline. From RHC we derived pulmonary artery pressures and cardiac output. From the MRI images we derived PA diameter and the diameter ratio of the PA and Ascending Aorta (rPAD/AAD).

Results

The PA diameter was significantly larger in PAH patient compared with non-PAH patients. ($p<0.001$). A ratio PAD/AAD>1 had a positive predictive value of 92% for PAH. Mean follow up time was 942 days. There was a significant dilatation during this follow-up ($p<0.001$). The change of the PA diameter did not correlate with the changes in pressure or cardiac output. A moderate correlation with follow-up time was found. ($r=0.56$, $p< 0.001$)

Conclusions

A dilatated pulmonary artery is useful for identifying PAH patients. However, during follow-up of PAH patients, progressive dilatation of the pulmonary artery is independent of the change in pulmonary artery pressure and cardiac output and might become independent from hemodynamics.

INTRODUCTION

Pulmonary Arterial Hypertension (PAH) is a clinical syndrome characterized by an increase in pulmonary vascular resistance leading to right heart failure and ultimately death.(1) Diagnosis early in the course of the disease is difficult because of the non-specific nature and symptoms like dyspnoea, exercise intolerance and fatigue. Several secondary effects of abnormally elevated pulmonary artery pressure on right sided structures, like pulmonary artery (PA) dilatation and right ventricular hypertrophy, may be helpful in the diagnosis of PAH. Pulmonary artery diameter (PAD) can be obtained non-invasively and is therefore one of the parameters in pulmonary hypertension which has been studied throughout the years. Early investigators have found reasonable correlations between right descending PAD and pulmonary artery pressure, using chest radiography (2). After the introduction of helical CT, several studies have been performed to measure the PAD, and showed that an increased main PAD is a reliable indicator of pulmonary hypertension, especially when the ratio of PAD and ascending aorta diameter (rPAD/AAD) is used. (3-9). More recently, using cardiac Magnetic Resonance Imaging (CMR), various authors showed that the PAD or its ratio with ascending aorta diameter is useful in the non-invasive detection of pulmonary

hypertension. Based on these studies it can be concluded that the PAD or the ratio with the ascending aorta diameter is useful in the non-invasive detection of pulmonary hypertension. However, correlations of diameter and pressure vary considerably between studies possibly due to differences in study populations. (10-14).
Although pulmonary artery pressure is supposed to be the driving force to dilate the pulmonary artery, the influence of other parameters such as time and flow is unknown. In addition it is unknown whether the changes in pulmonary artery pressure are followed by a similar change in diameter of the PA diameter. Therefore the aim of this study is to investigate in patients with PAH, if the change in PAD, over time, is a reflection of pressure and/or cardiac output changes.

MATERIALS AND METHODS

Study Group

This study is part of a large prospective study aimed to evaluate the role of MRI in PAH. This study has institutional review board approval and all patients where informed and gave their consent to the procedures. Fifty six patients with PAH were included in our study. All of these patients had a baseline evaluation before start therapy and a follow up evaluation of therapy at least 8 months separated in time. Each evaluation consists of a RHC and CMR measurement separated on average 2 days from each other. In 5 patients the quality of one of the MR Images, due to respiratory artifacts, did not permit measurements.

Consequently, 51 patients with PAH were included this study. All patients were classified in group 1 of the clinical classification of PAH(15); 41 patients with idiopathic PAH, 8 with collagen vascular disease associated PAH and 1 patient with HIV associated PAH. During follow-up patients where treated according to the standard in pulmonary hypertension. (table 7.1). Additionally, for baseline analysis, we included 18 patients suspected of having PH who underwent RHC and MR imaging once but had normal PA pressures at RHC (Normotensive subjects).

Treatment	No of Patients*
Ambrisentan	2
Bosentan	36
Sitaxentan	11
Calcium Channel blocker	3
Sildenafil	41
Epoprostenol (IV)	20
Treprostenil (SC)	13
Iloprost (INH)	1

Table 7.1 ***Treatment of the 51 patients with PAH***
**The total number of treatments exceeds the number of patients, indicating combined treatment or changes in treatment.*

CMR Imaging Protocol

In this study we used CMR images which were part of the routine clinical evaluation of the patients or part of former studies in this centre. CMR was performed with either a Siemens 1.5 T 'Sonata' or 'Avanto' whole body scanner (Siemens Medical Solutions, Erlangen. Germany) equipped with a phased-array body coil. PAD was assessed from magnitude images used for phase-contrast imaging, because these images were assessed in all patients in this retrospective study.(Figure 7.1) The image plane for measuring the ascending aorta was determined as follows: first a set of coronal localizer images was acquired, and then the image that showed the ascending aorta was selected. On this coronal image, a set of axial images was acquired that intersected the ascending aorta. From these axial images, the image was selected that showed the ascending aorta in a circular cross-section. This axial plane was at the level of the right pulmonary artery. During the follow-up acquisition, position of the orthogonal slice of the main PA at baseline measurements was used for positioning the orthogonal slice at follow-up of the main PA, to minimize differences in measurements localization from baseline.

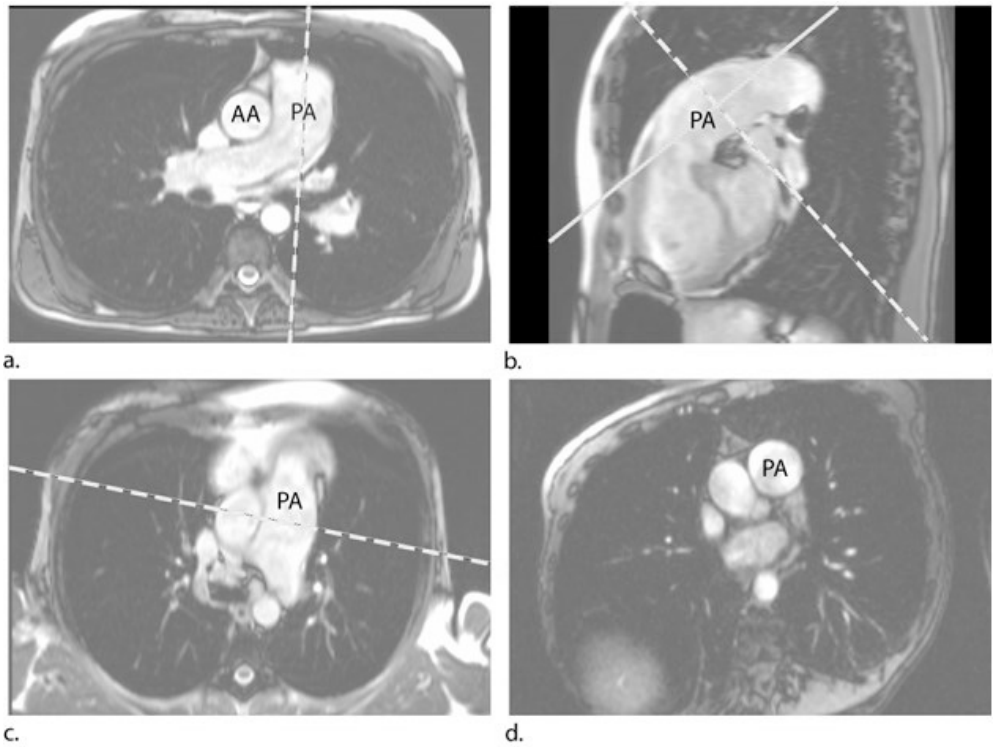

Figure 7.1: (a), (b) and (c) are steady-state free precession MR images to localize the pulmonary trunk (repetition time msec/echo time msec, 3.2/1.6; flip angle, 65°; section thickness, 6 mm; matrix, 256 × 96). First, an image was prescribed perpendicular to a transversal view (a) that included the pulmonary artery. This resulted in an oblique-sagittal image as shown in (**b**). A third localizer image shown in (c)was acquired according to the straight line in (b), and used together with (b) to obtain the image plane for the through-plane velocity measurement in the main pulmonary artery (PA). Image (d) shows the cross section of the main PA, acquired as the magnitude image in the flow measurement. This acquisition was with a gradient-echo sequence with through-plane phase-contrast velocity quantification (see text for details). In addition (**a)** shows also the plane orthogonal to the ascending aorta, in which the aortic diameter is measured that is used for normalization of the PA size with respect to the aorta. PA: Pulmonary Artery, AA: Ascending Aorta

Right Heart Catheterization

RHC was performed with a balloon, flow directed 7F Swan-Ganz catheter. The patients were in stable condition, lying supine and breathing room air, while heart rate was continuously monitored. Measurements were made of mean right atrial pressure, right ventricular pressure, systolic PA pressure (sPAP), diastolic PA pressure (dPAP), mean PA pressure (mPAP) and pulmonary capillary wedge pressure (PCWP). Cardiac Output (CO) obtained by either thermodilution or direct Fick method, from arterial- and mixed venous oxygen saturation and O2 consumption. Afterwards, Pulmonary Vascular Resistance (PVR) was calculated as (mPAP - PCWP)/CO. The median interval from CMR to right-sided heart catheterization was 2 days (range 2-21 days) .

Image Analysis

In the magnitude images the wall of the PA artery is automatically detected. A semi-automatic wall detection program, based on a study published by Li W. et al (16) using Matlab R2008a (The MathWorks, Natick, MA) was used to acquire more accurate measurements of the PA, reduce operator bias and minimize detection difficulties due to low signal intensity during diastole. Cross sectional area's (CSA) were obtained through the entire cardiac cycle (25 to 60 images) and visually checked by the operator. The minimal CSA was considered the diastolic CSA. From the cross sectional area of this contour the average diameter was calculated and used in this study. For scaling to aorta size we measured the diameter of the ascending aorta (AAD) in the same way as the PAD at end-diastole at the level of the PA bifurcation.

All analyses were performed by one investigator, unaware of RHC results. Ten patients were randomly selected and the measurements were repeated by both the first investigator and a second blinded investigator to test inter- and intra-observer variability.

Statistical Analyses

Hemodynamic values are presented as mean ± standard deviations or median (interquartile ranges). Differences between patient groups where evaluated with an independent sample t-test or a Mann-Whitney-U test when not normally distributed. The ability of the ratio of PA Diameter and Aorta Diameter (rPAD/AAD) to predict PAH was tested using a receiver-operating characteristic (ROC) curve. Differences between baseline and follow-up where evaluated with a paired sample t-test. For analysis of tertile differences a one-way ANOVA with post-hoc Bonferroni correction was used. Intra- and interobserver agreement was assessed by a Bland-Altman analysis. All tests where two-tailed and a P-value of <0.05 was considered significant. Analyses were performed with SPSS for Windows (version 15.0.0, SPSS Inc, Chicago Illinois)

RESULTS

RHC Results

RHC measurements confirmed the diagnosis of PAH in the 51 and normal pressures were found in the 18 normotensive subjects. The demographic and hemodynamic characteristics obtained at RHC of patients with PAH and normotensive subjects are given in table 7.2. As expected, mPAP, sPAP, dPAP, mean right atrial pressure, PVR and heart rate at RHC were significantly higher in patients with PAH compared to the normotensive subjects. In addition, cardiac output, cardiac index, stroke volume, and mixed venous oxygen saturation where significantly lower in patients with PAH. Between the PAH-group and the normotensive group there were no significant differences in terms of sex distribution, body surface area, arterial oxygen saturation or PCWP. The normotensive subjects were significantly older than the PAH group.

Parameter	Total	Patients with PH	Normotensive subjects	P Value *
No. of patients	69	51	18	...
Age (y)	44.8 ± 15	41.6 ± 13	53.7 ± 16.9	0.004
No of female patients ‡	53 (77)	38 (75)	15 (83)	ns.
Body surface area (m^2)	1.86 ± 0.21	1.90 ± 0.2	1.85 ± 0.16	ns.
Heart rate (beats/min)	83 ± 15	87 ± 14	73 ± 10	0.003
sPAP (mmHg)	66.6 ± 30.3	80.5 ± 21.9	27.1± 6.0	<0.001
dPAP (mmHg)	25.9 ± 13.2	32.2 ± 8.9	8.1 ± 3.7	<0.001
mPAP (mmHg)	42.2 ± 19.1	51.5 ± 12.5	15.9 ± 4.1	<0.001
Pulmonary capillary wedge pressure (mmHg)	8.2 ± 4.7	8.5 ± 5.1	7.3 ± 3.1	ns.
PVR (dynes/sec/cm)	660 ± 465	837 ± 401	130 ± 77	<0.001
Mean right atrial pressure (mmHg)	7.7 ± 5.2	8.9 ± 5.1	3.4 ± 2.1	<0.001
Right ventricle diastolic pressure	9.4 ± 6.9	11.4 ± 6.3	2.0 ± 2.4	<0.001
Cardiac Output (L/min)	5.3 ± 1.8	4.8 ± 1.65	6.7 ± 1.7	<0.001
Cardiac Index ($L/min/m^2$)	2.9 ± 1.1	2.6 ± 1.0	3.7 ± 1.0	<0.001
Stroke Volume (ml)	66.7 ± 27.4	55.8 ± 24.1	92.0 ± 22.1	<0.001
Arterial Oxygen saturation (%)	95.6 ± 3.0	95.6 ± 2.6	95.7 ± 4.3	ns.
Mixed venous oxygen saturation (%)	67.1 ± 9.1	65.2 ± 9.0	72.9 ± 6.5	0.002
PAD (mm)	31.9 ± 5.8	33.7 ± 5.3	25.0 ± 6.8	<0.001
AAD (mm)	28.3 ± 5.4	27.0 ± 4.4	31.8 ± 6.1	0.02
PAD/AAD	1.16 ± 0.27	1.26 ± 0.22	0.87 ± 0.17	<0.001

Table 7.2 ***Baseline Hemodynamic and demographic characteristics***

Unless otherwise indicated, data are means ± standard deviations or medians with interquartile ranges in parentheses
** Between PH Group an non-PH group ‡ Data in parentheses are percentages. PAD: Pulmonary Artery Diameter, AAD: Ascending Aorta Diameter*

PAD and pressure

The diastolic PAD was significantly larger in patients than in normotensive controls (table 7.2). In the entire group at baseline the correlation coefficient between PAD and mPAP was 0.58 ($p<0.001$, n=69) (Fig 7.2a). In patients with PAH (n=51), there was only a weak not significant relation (r= 0.29, p=0.04) between PAD an mPAP. A significant difference was found between the ratio of the PAD and the Ascending Aorta (rPAD/AAD) in the PAH-group and the group of normotensive subjects. The correlation coefficient of rPAD/AAD with the mPAP was 0.71 ($p<0.001$, n=69) (Fig 7.2b). Again for patients solely (n = 51) the relation between rPAD/AAD and dPAP was weaker (r = 0.49, $p<0.001$). The correlation coefficient of rPAD/AAD with diastolic instead of mean pulmonary artery pressure was 0.69. ($p<0.001$). The area under the receiver operating characteristic curve for the rPAD/AAD in the detection of PAH was 0.93 (CI: 0.86, 0.99) (Fig 7.3). The optimal rPAD/AAD was 1.1 with a sensitivity of 80% and a specificity of 94%. For an rPAD/AAD of 1 we found a sensitivity of 92% and a specificity of 72% and a positive predictive value (PPV) of 92 %

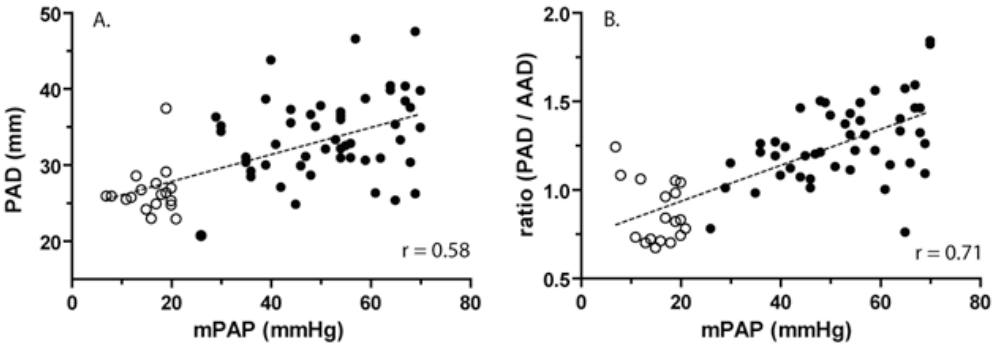

Figure 7.2 *Graph shows results of regression analysis in the study group for **a**) pulmonary artery diameter vs. mPAP and **b**) ratio of Pulmonary Artery Diameter / Ascending Aorta Diameter vs. mPAP. Open circles present normotensive subjects. Black dots represent PAH-patients.*

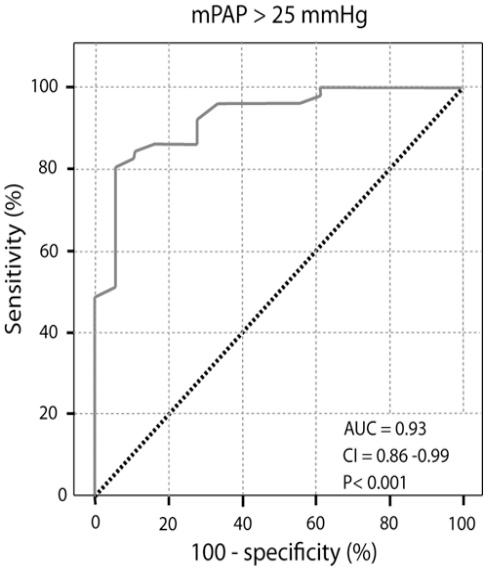

Figure 7.3 *The receiver-operating characteristic curve of the ability of the ratio rPAD/AAD to detect mean PA pressure > 25 mmHg. AUC = area under the curve; CI = confidence interval.*

Changes of PA diameter during follow-up

Mean follow-up time was 942 days (range 242 to 2359 days). During follow-up the diameter of the PA increased significantly. (See table 7.3). In 37 of 51 patients (73%) the diameter increased, with a mean of 3 mm ± 3mm (range 0.2– 17 mm). In the other 11 patients (22%) the diameter decreased with a mean of -2 mm ± 2 mm (range -0.2 – 5.4 mm). In three patients the diameter remained unchanged. PVR decreased and Cardiac Output increased, both significantly, during follow-up under treatment. (table 7.3). In figure 7.4 we plotted the change of PA diameter against the change in mPAP. Of the 11 patients with a decreased diameter in only 3 patients the decrease was more than 2 mm. The mPAP in these 3 patients was normalized or almost normalized under treatment; the mPAP at follow up ranged from 15-28 mmHg.

No. of patients	51		
Mean follow-up time (days)	942 (Range: 224-2359)		
Parameter	**Baseline**	**Follow-up**	**P-value***
Diameter PA (mm)	33.7 ± 5.3	35.7 ± 6.5	0.001
mPAP (mmHg)	51.5 ± 12.5	49.2 ± 13.9	0.15
Cardiac Output (L/min)	4.8 ± 1.65	5.2 ± 1.2	0.005
Heart rate (beats/min)	87 ± 14	83.5 ± 12.5	0.13
Stroke volume	55.8 ± 24.1	60.0 ± 23.3	0.6
PVR (dynes/sec/cm)	837 ± 401	730 ± 365	0.026

* Paired Sample T-test

Table 7.3 ***Hemodynamic characteristics and PA diameter at baseline and follow-up***

In patients with an increased PA diameter at follow-up the pressure either increased or decreased, and no relation was found between PA diameter change and pressure change. In figure 7.5 is shown that there were no significant difference between tertiles regarding CO, mPAP at baseline and PA diameter at baseline. In contrast, diameter change across tertiles of follow-up time differed significantly for the outermost tertiles, while the changes in CO and mPAP were not different over the tertiles. Overall a moderate correlation between follow-up time and diameter change was found ($r = 0.56$, $p < 0.001$). Neither a relation between changes in PAD and pulse pressure at baseline ($r = -0.21$, $p=0.14$), nor between changes in PAD and pulse pressure changes during follow-up ($r = 0.16$, $p=0.27$) was found.

Reproducibility of PAD measurements

Although the detection of the PAD is semi-automatic and the used program reduces operator bias, intra- and inter-observer variability was checked. At Bland-Altman analysis intra-observer (bias=0.1 mm, SD of bias=0.1 mm) and inter-observer variability (bias=0.1 mm, SD of bias 0.2 mm) showed good reproducibility of PAD measurements.

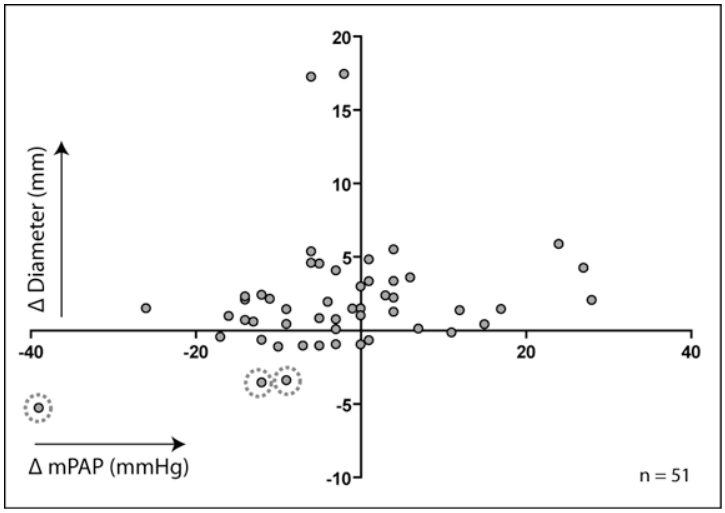

Figure 7.4 *Change in pulmonary artery diameter (ΔPAD) against the change in mean pulmonary artery pressure, (ΔmPAP), indicating the change in pressure and diameter between RHC + CMR evaluation in 59 patients. Four patients (highlighted) showed a decrease in diameter of more than 2 mm; in all four patients the pressure was (almost) normalized during follow-up*

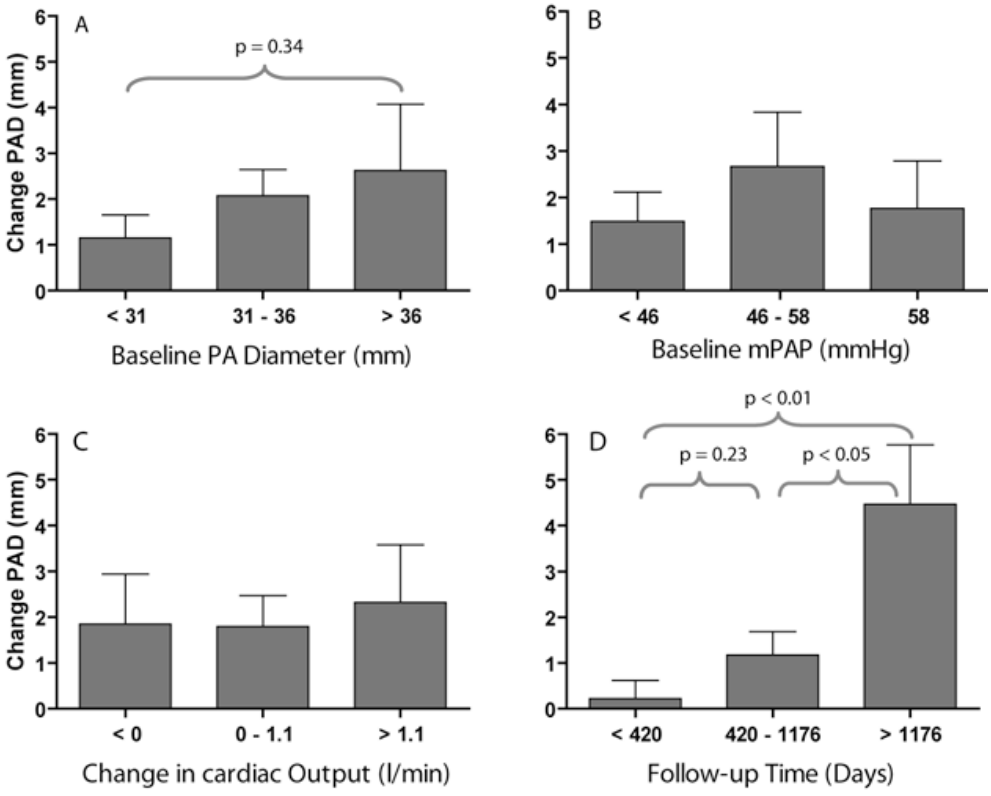

Figure 7.5 *Diameter change against the different tertiles of a.) PA diameter at baseline, b) mPAP at baseline, c) changes in cardiac output and d) duration of follow-up.*

DISCUSSION

In this study we show that PA diameter and its ratio with aortic diameter is useful in discriminating PAH-patients from normotensive subjects. This finding is in line with previous reports. However, during follow-up most pulmonary arteries show progressive dilatation, which is not related to the changes in pressure. Furthermore we found that the change in PA diameter was not related to changes in flow.

PAD and Pressure

Our results showed that the diastolic diameter of the PA has diagnostic value in PAH. We chose the diastolic diameter because this is the customary choice in CT-images. The used diameters were averaged diameters derived from the CSA. There was no difference in the relations of rPA/AA with diastolic pressure, mean pressure. This can be explained by the strong proportional relation between diastolic and mean pulmonary artery pressure (17, 18). The mPAP was used in this study since diagnosis is customarily based on it. As seen in prior studies we found that an enlarged PA diameter is related to the presence of PAH and thus can be used in the detection of PAH. We found that an rPAD/AAD > 1,1 yields the highest diagnostic accuracy. The use of the rPAD/AAD is also recommendable because it's relation with PAP is independent of BSA and sex (5). This cut-off point of 1.1 is different from earlier studies, which found that a ratio of 1 is the best diagnostic cut off point. The explanation of this discrepancy might be that these studies used 20 mmHg of mean PAP as diagnostic criterion for PAH, instead of the currently used criterion of 25 mmHg (1). However, if we apply the cut-off point of 1,0 a reasonable sensitivity of 92% and specificity of 72 % was found. The diagnostic accuracy of the rPAD/AAD might be overestimated since there is a relatively large hiatus in the levels of mPAP between the normotensive subjects and this well defined group of PAH- patients. In this study group, there were no subjects with aortic abnormalities or systemic hypertension, which could affect the size of the ascending aorta. Clearly, this is something that could affect the reliability of PAD/AAD.

Changes of PA diameter during follow-up

During follow-up the PA dilated in most of the patients. The changes of the diameter artery between the two cMRI measurements did not reflect changes in mPAP between the corresponding RHC's. In all the patients in whom the pressure was higher than initially the PA diameter had increased. However if the pressure was lower than initially, in the majority of this group the PA diameter had still increased. Only in three patients the PA diameter decreased more than 2 millimeters; in all these patients the pressure was normalized or almost normalized.

So, a progressive dilatation was found in these patients, which was not explained by pressure changes; even in the majority of the patients in which the pressure decreased there was an ongoing dilatation of the PA. Figure 7.5a suggests that a PA with large diameter at baseline tends towards greater dilatation during follow-up. It seems logical that if dilatation during follow-up becomes independent of hemodynamics, a larger diameter at baseline will lead to larger dilatation during the follow-up. This was, however, not found to be statistically significant The finding that neither pressure nor flow is related to the progressive dilatation in most of the patients, shows that other explanations than changes in pulmonary hemodynamics underlie this progressive dilatation. A phenomenon well known from the aneurysms of the aorta. Although systemic hypertension is an important

underlying cause of this disease, a further dilatation of the aorta in aneurysms is independent of systemic blood pressure (19). The main question was to investigate whether during follow-up changes in pulmonary artery dilatation exist and if they are related to changes in pressure . For this reason we did not evaluate specific other hemodynamic parameters as possible explanation for changes in pulmonary artery diameter. Nevertheless, we found that the diameter increase did not correlate with age, use of epoprostanol, and pulsatility in pulmonary artery diameter.
Absence of a direct relation between changes in pressure or flow and changes in diameter does not exclude that increased PAP or reduced flow is the cause of pulmonary artery dilatation. Although there is an absence of radiological studies investigating the structure of the pulmonary arterial wall, recent histological studies of the proximal parts of the pulmonary arteries provide evidence that significant remodelling of the proximal pulmonary arterial wall occurs in PAH. (20, 21). Structural changes in elastin and collagen under the influence of an increased pulmonary artery pressure (21) might eventually become a cause of pulmonary artery dilatation, irrespective of changes in pressure and flow. In addition, altered flow in PAH affects wall shear stress, and subsequently matrix properties of the vessel wall (22), which might lead to PA dilatation.

Clinical Implications

Our findings have several clinical consequences. First, the PA diameter, although useful in diagnosing PAH, is not useful for follow-up of the disease or evaluation of treatment effects. Secondly, we show that the dilatation of the PA in PAH is more related to follow-up time than to pressure change. This indicates that the pulmonary artery needs time to dilate. A severe dilated pulmonary artery at the time of diagnosis thus indicates that the pulmonary hypertension was already present for a long period of time. Thirdly, our data indicate that although increased pulmonary artery pressure leads to dilation of the pulmonary artery dilation, further dilation is a process most likely due to a change of the intrinsic vessel properties, which is independent of the pulmonary hemodynamics.

There are some limitations, which might influence our results. First, pressure and MRI measurements could not be performed simultaneously, for logistic and patient reasons. This might have effect on the strength of associations we found. However, given the average time of follow up (942 days) it is unlikely that a median interval of 2 days between right heart catheterization and MRI measurements affects the conclusions. Second, given the conus-shaped main PA, differences in level of image acquisition on the different time points might create a bias. We tried to overcome this by acquirement of all CMR images by one experienced investigator and by using reference points acquired at the baseline measurement during the follow-up measurement.
In conclusion, in patients with PAH, the ratio between PA diameter and ascending aorta diameter can be used for the detection of PAH. During follow-up, dilatation of the PA does not reflect changes in pressure or flow. Therefore changes in PA diameter cannot be used in clinical practice for the evaluation of the course of the disease, therapeutic response or as an estimator of the pressure.

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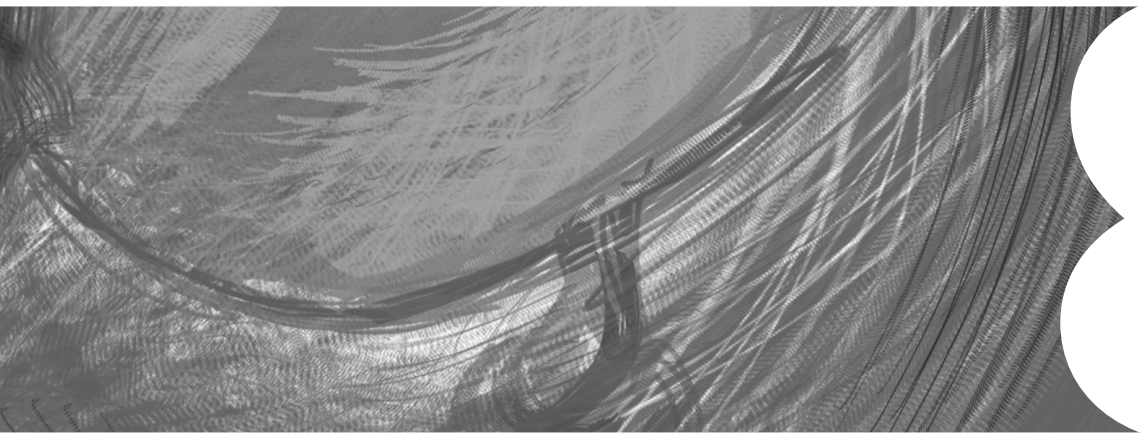
Summary, conclusions and implications



SUMMARY

One of the major complaints of patients with advanced chronic obstructive pulmonary disease (COPD) is an impaired exercise capacity and a limitation in daily activities. Elucidating the factors contributing to the exercise impairment is required to develop strategies to improve exercise capacity. Cardiac function during exercise is a potential target by which exercise capacity could be improved. Cardiac output in COPD can be affected in several ways. One well known complication of COPD is Pulmonary hypertension (PH). The effect of PH on exercise capacity, and through the frequently found excessive rise of pulmonary artery pressure during exercise, is largely unknown. If PH or the "exercise induced-PH", of which currently no definition exists, indeed contributes to exercise impairment, patients may benefit from pulmonary vasodilating therapy. There are, however, also other mechanisms by which cardiac output can be impaired in COPD. Understanding these mechanisms is important to develop strategies to improve cardiac output and, perhaps, exercise tolerance. The effect of lung hyperinflation and the associated increased pleural pressure swings, both induced by airflow limitation, on cardiac function received interest recently. The altered pulmonary mechanics are thought to adversely effect cardiac output by, among others, impairing venous return. The objective of this thesis was twofold. First, we wanted to elucidate how airflow limitation affects cardiac output in COPD via dynamic hyperinflation and increases in pleural pressure. Secondly, we wanted to investigate in which patients exercise is terminated due to a lowered cardiac output, as in these patients improving cardiac function could increase exercise capacity.

In Chapter 2 we showed that the high intrathoracic pressure which develops in patients with COPD hampers stroke volume during expiration. Although it was known that positive pressure *mechanical ventilation* can impair venous return and consequently cardiac output, this phenomenon this effect had not been shown in *spontaneously breathing* COPD-patients. We assessed the effects of intrathoracic pressure on pulmonary artery and right atrial pressure in twenty-one patients with stable COPD, at rest and during exercise. Beat-to-beat analysis of pulmonary artery pulse pressure during expiration showed that the high intrathoracic pressure hampers stroke volume by impairing venous return. The depressive effect of intrathoracic pressure on stroke volume persisted during exercise. Patients with a low right atrial filling pressure showed the largest negative effects of an increased expiratory intrathoracic pressure on stroke volume.
The sometimes impressive effect of severe airflow limitation on the pulmonary circulation was further illustrated in the appendix of Chapter 2, where we described the pressure changes in the pulmonary artery, right ventricle, right atrium, oesophagus and radial artery during spirometry in a patient with severe COPD. The maximal expiration acted as a Valsalva maneuver which impaired venous return, thereby severely reducing right ventricular stroke volume and subsequently left ventricular stroke volume and systemic blood pressure until the next inspiration.
Because we found evidence of significant negative effects of a high intrathoracic pressure during expiration on cardiac function, we wanted to evaluate whether we could improve cardiac function by reducing expiratory intrathoracic pressure. In the study described in chapter 3 we measured stroke volume in patients at rest and during exercise, both while breathing room air and while breathing a helium-oxygen mixture (Heliox). This mixture is known to improve airflow and reduce expiratory intrathoracic pressure in COPD-patients.

We confirmed that a reduction in intrathoracic pressure with heliox improves stroke volume at rest. This provided additional evidence that cardiac function is indeed adversely affected by airflow limitation. Interestingly, the improvement did not last during exercise, which suggests that a relatively small change in intrathoracic pressure is not sufficient to affect exercise cardiac output in COPD.

In Chapter 4 we showed that the marked increases in expiratory intrathoracic pressure can lead to significant errors in measurements of mean pulmonary artery pressures (mPAP) during exercise, when pressures are measured at end-expiration. Incorrect estimation of mPAP led to a wrong diagnosis in a substantial part of the patients. Averaging pulmonary pressure over the full respiratory cycle and a correction for intrathoracic pressure (estimated using a right atrial pressure waveform) resulted in a better but still imperfect estimation of intravascular pressure. The effect of intrathoracic pressure was similar on mPAP and pulmonary capillary wedge pressure (PCWP). Therefore, the transpulmonary pressure gradient and pulmonary vascular resistance are not affected by intrathoracic pressures as long as mPAP and PCWP are measured at the exact same time point in the respiratory cycle. Including pulmonary vascular resistance in the definition of exercise induced pulmonary hypertension therefore avoids misdiagnosis if intrathoracic pressure or PCWP is taken into account.
In chapter 5, an integrated approach consisting of cardiopulmonary exercise testing and right heart catheterisation at rest and during exercise was used to identify a subgroup of COPD patients in whom the presence of PH impaired exercise tolerance. We describe the ventilatory and cardio-circulatory exercise profiles of forty-seven COPD patients divided in three subgroups, no PH, moderate PH and severe PH. We were able to demonstrate that only patients with severe PH showed at the end of exercise evidence of exhaustion of the cardiac reserve in combination with a continuing ventilatory reserve. In patients with no or only moderate PH, exercise termination was associated with an exhausted ventilatory reserve and evidence of a cardio-circulatory reserve. This implies that only in patients with severe PH, defined as a resting mean pulmonary artery pressure above 40 mmHg, exercise capacity might improve with therapeutic interventions aiming to reduce pulmonary artery pressure.
The complexity of the interactions between cardiac function and pulmonary function in COPD is further exemplified in chapter 6. We describe the cases of two patients suffering from severe COPD in combination with a patent foramen ovale. In both cases, hypoxemia due to right-to-left shunting aggravated the degree of PH, whereas the presence of PH by itself worsened right-to-left shunting and hypoxemia. The vicious circle of PH and hypoxemia was felt to significantly worsen the degree of dyspnea in both patients, and was therefore interrupted in two different ways. In the first patient, the foramen ovale was closed during a percutaneous intervention. In the second patient, the pulmonary artery pressure was pharmacologically reduced, which resulted in a physiological closing of the patent foramen ovale. A dramatic improvement of symptoms was noted in both patients.
In chapter 7 we evaluated in fifty-one patients with pulmonary arterial hypertension without evidence of parenchymal lung disease how pulmonary hypertension affects the size of the pulmonary arteries. We found that the ratio of the diameters of the pulmonary artery trunk and ascending aorta is useful for the detection of PH, with a positive predictive value of 92% when the ratio is greater than 1. The pulmonary artery exhibited progressive

dilatation during follow-up, but the change in pulmonary artery diameter was not related to changes in pulmonary artery pressure of blood flow. This implies that measuring the pulmonary artery diameter is useful for the detection of PH, but not for the evaluation of disease progression or therapeutic responses.

CONCLUSIONS AND IMPLICATIONS

Pulmonary hypertension and pulmonary vasodilating therapy in COPD

The identification of those patients whose exercise capacity is limited by pulmonary hypertension (chapter 5) is an important step forward in identifying COPD patients who may benefit from pulmonary vasodilating therapy. Previous trials using pulmonary vasodilators in COPD included patients with less severe pulmonary hypertension and showed no beneficial effects of therapy on exercise capacity [1,2,3]. Our study shows that only patients with out-of-proportion pulmonary hypertension may be candidates for trials of using PAH specific drugs. Such a study in these patients is therefore justified.

Whether pulmonary hypertension during exercise matters is debatable. Recently, emphasis is put on the slope of mPAP increase related to cardiac output increase with exercise. [4,5] Future studies should evaluate whether an increased slope of mPAP contributes to exercise intolerance and whether it can lead to identification of more patients who potentially benefit from vasodilating therapy. Therefore, measurement of the mPAP/cardiac output slope combined with measures of ventilatory and circulatory reserves at the end of exercise are needed. This is especially interesting in patients with borderline elevated pulmonary artery pressure at rest and less severe airflow limitation. In these patients the ventilatory problems may be less overwhelming, thereby creating a potential role for the pulmonary circulation in limiting exercise.

Diuretic use in COPD

In the past, the low stroke volume in COPD was mainly attributed to an increased right ventricular afterload. The normal response to maintain right ventricular output when the afterload is increased, is to increase preload. In chapter 2, 2a and 3 we found signs of an impaired right ventricular preload in COPD-patients without overt pulmonary hypertension. This is the consequence of the high intrathoracic pressures (chapter 3) and hyperinflation [6]. A higher venous or right atrial pressure is necessary to maintain sufficient venous return. The use of diuretics, frequent in COPD, may interfere with this compensatory mechanism [7]. Tailored use of diuretics might therefore be necessary for an optimal cardiac function in COPD-patients, and a study is required and advised.

Hemodynamic measurements during exercise in COPD

We showed in chapter 3 that increased intrathoracic pressure during exercise results in a marked overestimation of intravascular pressure when pulmonary artery pressure is measured at end-expiration. We therefore recommend to average pulmonary artery pressure over the respiratory cycle, when invasive hemodynamic measurements are performed during exercise. It is therefore advised that pulmonary vascular resistance should be added to the definition of exercise induced pulmonary arterial hypertension, as its determination is not affected by intrathoracic pressure.

Patent foramen ovale in COPD

In chapter 6 we showed that the combination of COPD and a patent foramen ovale (PFO) can lead to severe complaints in some patients. It is therefore tempting to state that, when present, closure of a PFO should be considered in COPD. It is however debated whether a PFO affects dyspnea and exercise tolerance in the general COPD population [8,9] and a PFO might even be beneficial in more severe pulmonary hypertension [10]. We therefore need more information about the prevalence and relevance of PFO's in COPD, before we start studying the effects and risks of PFO closure.

Pulmonary artery dilatation

Pulmonary artery dilatation was shown as an inevitable consequence of long-standing pulmonary hypertension, and was even persisting when treatment effectively reduced pulmonary artery pressure (chapter 7). Some rare but severe consequences of pulmonary artery dilatation might complicate pulmonary hypertension. Rupture [11] and dissection [12] of the pulmonary artery and also compression of the coronary arteries [13] or bronchi [14] are all described in pulmonary hypertension and may explain why pulmonary artery dilatation is related to sudden death in pulmonary hypertension [15]. As some are treatable, Higher awareness of the complications of pulmonary artery dilation is indicated and may contribute to a better survival in pulmonary hypertension.

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Samenvatting

SAMENVATTING

Een van de belangrijkste klachten van patiënten met COPD (*chronic obstructive pulmonary disease*) is een verminderd vermogen tot het leveren van lichamelijke inspanning en daardoor een beperking van de dagelijkse activiteiten. Het is daarom van belang om te weten welke factoren bijdragen aan het slechte inspanningsvermogen van deze patiënten om strategieën te ontwikkelen om het inspanningsvermogen te verbeteren. De cardiale functie is een potentieel doel, aangezien deze kan zijn afgenomen in COPD-patiënten om verschillende redenen. Een bekende complicatie van COPD is pulmonale hypertensie. Het effect van pulmonale hypertensie op het inspanningsvermogen, en ook van de excessieve stijging van de druk inde pulmonaal arterie tijdens inspanning, is grotendeels onbekend. Er zijn echter nog meer mechanismen waarop de cardiale functie (hartminuutvolume) kan worden benadeeld in COPD. Het is belangrijk om deze mechanismen te begrijpen om het hartminuutvolume te kunnen vergroten en zodoende mogelijk het inspanningsvermogen te vergroten. Het effect van hyperinflatie van de longen en de daarmee geassocieerde stijging van de intrathoracale druk, beide een gevolg van luchtwegobstructie, op de cardiale functie heeft recent veel aandacht gekregen in de literatuur. Er wordt veronderstelt dat deze veranderde longmechanica een negatief effect hebben op het hartminuutvolume, onder andere doordat de veneuze return wordt belemmerd. Het doel van dit proefschrift was tweeledig. Ten eerste wilden we ophelderen hoe luchtwegobstructie het hartminuutvolume benadeeld in COPD , door middel van dynamische hyperinflatie en de verhoging van de intrathoracale druk. Ten tweede wilden we uitzoeken bij welke COPD-patiënten het inspanningsvermogen is gelimiteerd door het verlaagde hartminuutvolume, omdat dit de patiënten zijn waarin verbetering van de cardiale functie kan leiden tot een verbetering van het inspanningsvermogen.

In hoofdstuk 2 hebben we laten zien hoe een hoge intrathoracale druk die zich ontwikkelt in patiënten met COPD het slagvolume tijdens uitademing belemmerd. Het was bekend dat een hoge druk bij mechanisch beademde patiënten de veneuze return en daarmee de cardiac ouput verminderd. Het was nog bekend dat ditzelfde mechanisme ook bij spontaan ademende COPD-patiënten ook rol speelt. We hebben hier de effecten van de intrathoracale druk op de druk in de pulmonaal arterie in kaart gebracht in 21 patiënten met COPD. Door een slag-op-slag analyse van de polsdruk in de pulmonaal arterie tijdnes uitademing konden we laten zien dat een hoge intrathoracale druk leidt tot een afname van het slagvolume door een verminderde veneuze return. De negatieve effecten van de intrathoracale druk op het slagvolume bleven ook bij inspanning bestaan. Bij patiënten met een lage veneuze of rechter atrium druk was het effect van de intrathoracale druk op het slagvolume het grootst.

Hoe indrukwekkend het effect luchtwegobstructie op de longcirculatie kan zijn hebben we verder geïllustreerd in de appendix van hoofdstuk 2, waar we een beschrijving geven van de drukverandering in de pulmonaal arterie, rechter ventrikel, rechter atrium, slokdarm en de arteria radialis tijdens spirometrie in een patiënt met ernstig COPD. De geforceerde uitademing gedroeg zich als een Valsalva-manoeuvre die de veneuze return sterk verminderde, waardoor een sterke reductie van het slagvolume van de rechter ventrikel and vervolgens van de linker ventrikel en systemische bloeddruk tot aan de volgende inademing. Omdat we in hoofdstuk twee aanwijzingen hadden gevonden voor een significant effect van de hoge intrathoracale druk tijdens uitademing op de cardiale functie, wilden we ook onderzoeken of we de cardiale functie konden verbeteren door de intrathoracale druk te

verlagen. In the studie die beschreven is in hoofdstuk 3 hebben we het slagvolume gemeten in patiënten in rust en tijdens inspanning, zowel in kamerlucht als tijdens het gebruikt van een helium-zuurstof mengsel (Heliox). Van Heliox is bekend dat het de luchtstroom verbeterd en de intrathoracale druk tijdens uitademing verlaagd in COPD-patiënten. Hier konden we bevestigen dat een afname van de intrahoracale druk in rust leidde tot een verbetering van het slagvolume. Minstens zo interessant was dat deze verbetering geen stand hield tijdens inspanning. Dit suggereert dat een kleine verandering in de intrathoracale druk, zoals wij die tot stond konden brengen, niet genoeg is het om het slagvolume tijdens inspanning te verbeteren.

In hoofdstuk 4 laten we zien dat de excessieve stijging van de pulmonaal arterie druk tijdens uitademing kan leidden tot significante fouten in de bepaling van de gemiddelde pulmonaal arterie druk tijdens inspanning. Een foutieve bepaling van de gemiddelde pulmonaal arterie druk leidde to verkeerde diagnose in een belangrijk deel van de patiënten. Het middelen van de druk over enkele volledige ademhalingscycli resulteerde in betere, maar nog steeds niet perfecte, bepaling van de intravasculaire druk. Het effect van de intrathoracale druk op de pulmonaal arterie druk was gelijk aan het effect op de wiggedruk. Daardoor zijn de transpulmonale gradiënt en de pulmonary vascular resistance onafhankelijk van de druk in de thorax zolang de druk in de pulmonaal arterie en de wiggedruk maar op exact hetzelfde tijdspunt in de ademhalingscyclus gemeten worden. Het is daarom wenselijk om de pulmonay vascular resistance in de definitie van inspanningsgebonden pulmonale hypertensie op te nemen. Dit voorkomt foutieve diagnoses in patiënten waarin de intrathoracale druk is verhoogd tijdens inspanning.

In hoofdstuk 5 hebben een door gebruik te maken van zowel inspanningstesten en rechter hartkatheterisatie in rust en tijdens inspanning een subgroep van COPD-patiënten geidentificeerd bij wie de aanwezigheid van pulmonale hypertensie bepalend was voor het slecht inspanningvermogen. We beschrijven hier de ventilatoire en cardiale respons bij inspanning in 47 COPD-patiënten die we opgedeeld hebben in drie subgroepen: 1) zonder pulmonale hypertensie, 2) matige pulmonale hypertensie en 3) ernstige pulmonale hypertensie. Hiermee konden we laten zien dat allen in de groep met ernstige pulmonale hypertensie er bewijs is voor de afwezigheid van cardiale reserve in combinatie met een aanwezige ventilatoire reserve. In patiënten zonder pulmonale hypertensie of met matige pulmonale hypertensie bestond een cardiale reserve in combinatie met een afwezige ventilatoire reserve. Dit alles impliceert dat alleen in patiënten met ernstige pulmonale hypertensie, gedefinieerd als een druk in de pulmonaal arterie in rust hoger dan 40 mmHg, het inspanningsvermogen mogelijk verbeterd kan worden door therapeutische interventies gericht op het verlagen van de druk in de pulmonaal arterie.

Hoe complex de interactie tussen hart en long kan zijn in COPD hebben we laten zien aan de hand van twee voorbeelden in hoofdstuk 6. We beschrijven twee patiënten met ernstig COPD in combinatie met een patent foramen ovale. In beide casus leidde de hypoxemie, die veroorzaak door een rechts-links shunt over het foramen ovale, tot een verergering van de aanwezige pulmonale hypertensie. De pulmonale hypertensie leidt echter weer tot een verergering van de recht-links shunt en hypoxemie. Deze vicieuze cirkel van pulmonale hypertensie en hypoxemie leidde tot een significantie verslechtering van de kortademig-

heid in beide patiënten. Er werd daarom besloten tot interventie gericht op het foramen ovale. Bij de eerste patiënt werd besloten het foramen ovale te sluiten door middel van percutane interventie. Bij de tweede patiënt werd de druk in de pulmonaal arterie farmacologisch verlaagd, wat leidde tot een fysiologische sluiting van het foramen ovale. Een indrukwekkende verbetering van de klachten trad op in beide patiënten.

In hoofdstuk 7 hebben in 51 patiënten met pulmonale arteriële hypertensie zonder afwijkingen in het longparenchym geëvalueerd hoe de pulmonale hypertensie de diameter van de longslagader beïnvloed. We vonden dat ratio van de diameters van de truncus pulmonalis en de aorta ascendens erg bruikbaar is voor de detectie van pulmonale hypertensie. De positief voorspellende waarde van een ratio >1 was 92%. Echter, tijdens follow-up bestond er een progressieve dilatatie van longslagader in nagenoeg alle patiënten,die niet gerelateerd was aan veranderingen in de druk of in de bloedstroom. Dit houdt in dat de het meten van de longslagader nuttig is in het opsporen van pulmonale hypertensie, maar zeker niet geschikt is om ziekteprogressie of therapierespons te monitoren

CONCLUSIES

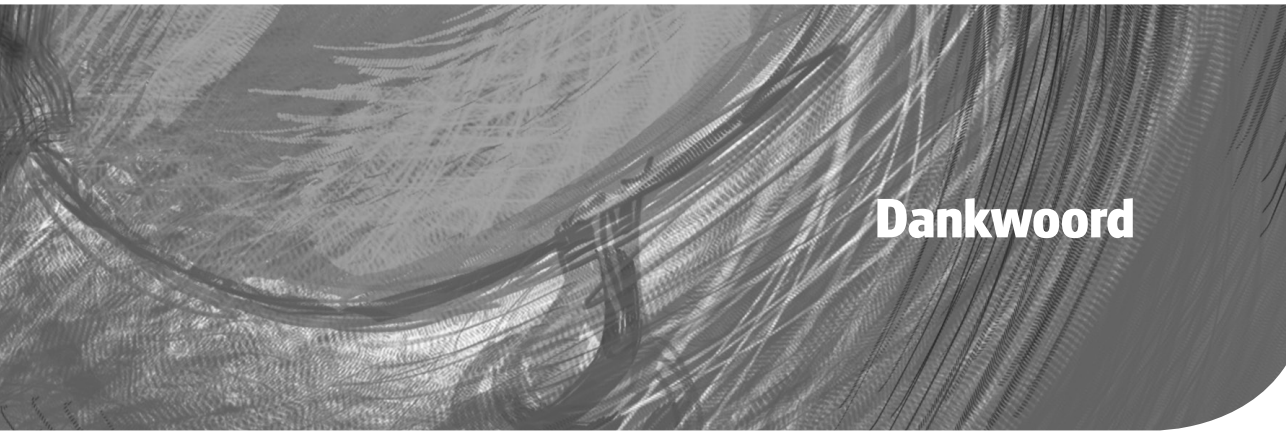
Een belangrijk conclusie is dat het slagvolume van patiënten door verschillende manieren kan worden beïnvloed. De verschillende mechanismen behoeven een verschillende strategie om de cardiale functie te verbeteren. In het verleden werd het lage slavolume in COPD met name toegeschreven aan een verhoogde rechterventrikel belasting door pulmonale hypertensie. Wij hebben in hoofdstuk 2,2a en 3 laten zien dat ook een (onder) vulling van de rechterventrikel een belangrijk rol speelt. Toekomstig onderzoek zou gericht moeten zijn op het verbeteren van de vulling van de rechter ventrikel. Dit zou kunnen door het verlagen van de intrathoracale druk, danwel door een hogere veneuze druk bijvoorbeeld oor het gebruik van diuretica in stabiel COPD-patiënten te verminderen.
Een andere, zeer belangrijke, conclusie van dit proefschrift is dat er een subgroep van COPD- patiënten is bij wie de pulmonale hypertensie bepalend is voor het inspanningsvermogen. In deze groep, met ernstige pulmonale hypertensie, kan behandeling van de pulmonale hypertensie dus leidden tot een beter inspanningsvermogen. Een toekomstige trial met pulmonaal vasodilaterende medicatie is dan ook gerechtvaardigd en gewenst in deze groep patiënten.

Abbreviations

ABBREVIATIONS

AA	ascending aorta
AAD	ascending aorta diameter
BR	breathing reserve
CI	cardiac index
CMR	cardiac magnetic resonance
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPET	cardio-pulmonary exercise test
DLCO	diffusion capacity for carbon monoxide of the lungs
dPAP	diastolic pulmonary artery pressure
FEV1	forced expiratory volume in the first second
fR	respiratory frequency
HFpEF	heart failure with preserved ejection fraction
HR	heart rate
HRCT	high resolution computed tomography
ITP	Intrathoracic pressure
mPAP/Q	slope relating rise in mPAP with rise in cardiac output
mPAP	mean pulmonary artery pressure
mPAPaveraged	mean pulmonary artery pressure averaged over the respiratory cycle
mPAPend-exp	mean pulmonary artery pressure at end-expiration
mPAPtm	transmural pulmonary artery pressure
MRI	magnetic resonance imaging
MVV	maximal voluntary ventilation
NO	nitric oxide
PA	pulmonary artery
PaCO2	arterial carbon dioxide tension
PAD	pulmonary artery diameter
PAH	pulmonary arterial hypertension
PaO2	arterial oxygen tension
PCWP	pulmonary capillary wedge pressure
PCWPaveraged	pulmonary capillary wedge pressure averaged over the respiratory cycle
PCWPend-exp	pulmonary capillary wedge pressure at end-expiration
PCWPtm	transmural pulmonary capillary wedge pressure
Peso	esophageal pressure
PetCO2	end-tidal carbon dioxide tension
PFO	patent foramen ovale
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RAP	right atrial pressure
RAPnadi	lowest point of right atrial pressure
RAPswing	difference in right atrial pressure between inspiration and expiration
RHC	right heart catheterisation

ROC	receiver operating characteristic
rPAD/AAD	ratio of the pulmonary artery diameter and ascending aorta diameter
RV	right ventricle
RVP	right ventricular pressure
SaO2	arterial oxygen saturation
sPAP	systolic Pulmonary Artery Pressure
SVC	slow vital capacity
SVI	stroke volume index
SvO2	mixed venous oxygen saturation
TLC	total lung capacity
VA	alveolar volume
VC	vital capacity
VE/CO2-slope	mean regression slope relating minute ventilation to carbon dioxide production
VEmax	maximal ventilation
VO2	oxygen consumption
Vt	tidal volume



Dankwoord

Dankwoord

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About the author

Bart Boerrigter was born on march 18, 1984 in Denekamp, The Netherlands. In 2002, he graduated from secondary school (athenaeum) at the Carmel College in Oldenzaal. Subsequently he began studying Medicine at the University of Groningen. He developed a special interest in pulmonary medicine and after an internship pulmonary medicine in Yokyakarta, Indonesia, he started a PhD trajectory in 2009 under supervison o Prof. Dr. Anton Vonk Noordegraaf. The results of which are presented in this thesis. In 2012, Bart spent one month in Boston to work on one of his PhD projects under the supervision of Dr. David Systrom and Dr. Aaron Waxman at Brighams and Women's Hospital, Harvard Medical School. He presented the work of this thesis at national and international conferences. In December 2012, he started working as a resident at the department of internal medicine of the Onze Lieve Vrouwe Gasthuis in Amsterdam, as part of his specialization in pulmonary medicine.